UKALL 2011 Trial Considerations
Rochelle Lowe – Clinical Nurse Specialist
Preliminary results February 2010

• Patients eligible for study 2522
• Deaths in induction 25
• Non-relapse deaths 82
• Relapses 124

• Patients randomised
  408 high risk, 521 low risk
Preliminary results continued

High risk
   2 years 92.9%, 3 years 90.5%, 4 years 87.4%, 5 years 86.1%

Low risk
   2 years 99%, 3 years 98.7%, 4 & 5 years 98.4%

Other
   2 years 93.8%, 3 years 92.7%, 4 years 92.2%, 5 years 91.5%
UKALL 2011

- Phase III randomised trial for patients with Acute Lymphoblastic Leukaemia (ALL) and Lymphoblastic Lymphoma (LBL) aged 1-25 years

- Recruitment target: 2640 patients

- Opened 26th April 2012
UKALL 2011 OBJECTIVES

- To reduce toxicity through introduction of a short 14-day course of high dose dexamethasone in lieu of the conventional lower dose given for 28 days in induction

- To provide more effective CNS prophylaxis and reduce burden of therapy through introduction of high dose methotrexate and by omission of vincristine and dexamethasone pulses and continuing intrathecal therapy in maintenance

- To decrease toxicity and reduce burden of therapy by administering a single delayed intensification to all patients and limiting augmented therapy to those who are not MRD Low Risk.
STAGES OF TREATMENT

1) Induction
2) Consolidation
3) Interim maintenance
4) Delayed Intensification
5) Maintenance

R1
R2
INCLUSION CRITERIA (R1)

- Patients from age 1 (first birthday) to 24 years 364 days (at time of diagnosis) with a first diagnosis of acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma (LBL) diagnosed using standard criteria

- Written informed consent

- Negative pregnancy test within 2 weeks prior to starting treatment for female patients of childbearing potential
EXCLUSION CRITERIA (R1)

- Infants less than a year old at diagnosis

- Patients diagnosed with B-ALL (Burkitt-like, t(8;14), L3 morphology, SMIg positive)

- Patients diagnosed with Philadelphia-positive ALL

- Patients in whom written informed consent has not been obtained from parents and/or patients prior to randomisation
EXCLUSION CRITERIA (R1) CONT'D.

• Patients who have received previous treatment for ALL or LBL
  – EXCEPTION: patients who have received dexamethasone treatment for no more than 7 days (due to clinical urgency) immediately prior to randomisation

• Patients who are sexually active and unwilling to use adequate contraception during therapy and for one month after last trial treatment
INDUCTION

Standard induction treatment:

• 3 drug induction (Regimen A)
• 4 drug induction (Regimen B)
• Allocated by clinician based on risk group determined by factors such as disease type, (T-ALL, LBL), age, cytogenetics, Down’s syndrome etc.
• Induction lasts 5 weeks for all patients

R1 will test different dexamethasone dosing
B-CELL PRECURSOR ALL (BCP ALL)

• NCI Standard Risk
  – Patients aged ≥ 1 year and <10 years at diagnosis and with a highest WCC count before starting treatment of <50x10⁹/L
  RECEIVES REGIMEN A INDUCTION

• NCI High Risk
  – Patients aged ≥10 years at diagnosis and/or with a diagnostic WCC ≥50x10⁹/L
  RECEIVES REGIMEN B INDUCTION
T-CELL ALL AND ADVANCED LBL

• All patients with T-cell ALL receive REGIMEN B INDUCTION

• All patients with LBL receive REGIMEN B INDUCTION
DOWN’S SYNDROME PATIENTS

• All DS patients receive REGIMEN A induction
• If Day 15 bone marrow shows a slow early response (≥25% blasts at day 15) and in absence of serious morbidity, DS patients switch to Regimen C induction on day 15.
• Not eligible for R2
• Guidelines for further treatment
Minimal residual disease (MRD)

- 10% - 15% of good risk children will relapse
- Strongest predictor of outcome is response to therapy
- New ALL $10^{12}$ malignant cells
  Remission <5% blasts = $10^{10}$ undetectable cells
- MRD 100 fold increase in sensitivity
- Predict those that could be *cured* with less therapy
- Identify those at high risk of relapse that may benefit from more therapy
R1 RANDOMISATION

• All patients randomised to receive either:
  – Standard dexamethasone
    • 6mg/m\(^2\)/day for 28 days
  – Short dexamethasone
    • 10mg/m\(^2\)/day for total of 14 days
    • Split dosing for patients aged \(\geq\) 10 years
DAY 8/15 BONE MARROW

• BM test on day 8 for all ALL patients
• BM test of day 15 for Regimen A patients whose bone marrow show >25% blasts on day 8.
• Day 8/15 result used to stratify treatment in cases of MRD failure/No result.
DAY 29

• Minimal Residual Disease (MRD) Test for ALL patients.
  – MRD sample sent to MRD laboratory as per protocol

• Tumour volume assessment for LBL patients

• Further treatment allocated based on result of day 29 test.
DAY 29 – ALL PATIENTS

- MRD Low Risk
  - MRD <0.005%
  - Continue Regimen A or B as previous assigned
  - No further MRD measurement
  - Eligible for R2

R2 randomisation should be performed as soon as possible after obtaining day 29 MRD Result and after Informed Consent obtained.
DAY 29 – ALL PATIENTS

• MRD Risk
  – MRD $\geq 0.005\%$
  – Receive Regimen C consolidation
  – Week 9 MRD Test (result not given to clinician)
  – Further MRD measurement upon recovery from consolidation at week 14

Await week 14 MRD Result
WEEK 14 MRD

For MRD Risk Patients:

- **MRD Intermediate Risk**
  - MRD <0.5%
  - CONTINUE REGIMEN C
  
  R2 randomisation should be performed as soon as possible after obtaining Week 14 MRD Result and after Informed Consent obtained.

- **MRD High Risk**
  - MRD ≥0.5%
  - Taken off UKALL 2011 protocol treatment
DAY 29 – ALL PATIENTS

• MRD No Result
  – Inadequate sample or no MRD marker
  – Approx 7% patients
  – Further therapy determined by early response as assessed by morphology:
    • Slow Early Response (SER): Receive regimen C consolidation and continue Regimen C
    • Rapid Early Response (RER): continue Regimen A or B as assigned for induction.

No further MRD required. Perform R2 randomisation as soon as possible
R2 RANDOMISATION

• Factorial randomisation affecting treatment in 2 phases:
  – Interim maintenance phase
  – Maintenance phase

• Inclusion in the second part of the trial requires consent to participate in both elements of R2.
R2 RANDOMISATION – IM PHASE

• Patients randomised to received either:
  – Standard Interim Maintenance
    • For Reg C patients this is Capizzi Interim Maintenance
      or
  – High dose methotrexate
    • For Regimen A/B: Protocol M
    • For Regimen C: Protocol M-A
AALL0232: DH vs. PH in Patients 1-9.99 Years Old
Winick, ASCO 2011

Interaction between steroid and MTX questions, so outcome examined on the superior HD MTX arm
R2 RANDOMISATION – MAINTENANCE PHASE

• Patients randomised to received either:
  – Maintenance with pulses
    • This is the standard maintenance treatment for patients with ALL
    • Patients receive ‘pulses’ of dexamethasone and vincristine
  – Maintenance without pulses
    • Experimental arm with removal of the ‘pulses’ normally given in the maintenance phase of treatment
Example shown is for Regimen A
EXCLUSION CRITERIA (R2)

- MRD High Risk ALL patients and LBL patients with a poor response
- Patients with significant renal impairment (renal function outside of normal limits corrected for age), pleural effusion or ascites
- Previous history of methotrexate encephalopathy
- MRD Intermediate Risk patients with history of pancreatitis
EXCLUSION CRITERIA (R2) CONT'D.

- Candidates for allogeneic SCT in CR 1
- Down’s syndrome patients
- Prior cranial irradiation
- M3 marrow at day 29
<table>
<thead>
<tr>
<th>Phase of treatment</th>
<th>Regimen</th>
<th>IMP</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>A,B,C</td>
<td>dexamethasone</td>
<td>Tablets or syrup (or injection*)</td>
</tr>
<tr>
<td>Standard Interim</td>
<td>A,B</td>
<td>dexamethasone, vincristine, mercaptopurine, oral methotrexate, intrathecal methotrexate</td>
<td>Tablets or syrup</td>
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<tr>
<td>Maintenance</td>
<td></td>
<td></td>
<td>Injection</td>
</tr>
<tr>
<td>Protocol M</td>
<td>A,B</td>
<td>mercaptopurine, intravenous methotrexate, intrathecal methotrexate</td>
<td>Tablets or IMP oral suspension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Injection</td>
</tr>
<tr>
<td>Capizzi Maintenance</td>
<td>C</td>
<td>vincristine, intravenous methotrexate, pegasparagase / crisantaspase*</td>
<td>Injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Injection</td>
</tr>
<tr>
<td>Protocol M-A</td>
<td>C</td>
<td>mercaptopurine, intravenous methotrexate, intrathecal methotrexate, pegasparagase / crisantaspase*</td>
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<td></td>
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<td></td>
<td>Injection</td>
</tr>
<tr>
<td>Maintenance</td>
<td>A,B,C</td>
<td>vincristine, dexamethasone, intrathecal methotrexate</td>
<td>Injection</td>
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<td>Tablets or syrup</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Injection</td>
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</tbody>
</table>
RECRUITMENT TO R1

• 304 patients randomised as of 23.06.2013
• 233 patients randomised at data freeze DMC (29.04.13)
  – 223 ALL, 10 LBL
  – 86 potential patients have not entered the trial
    • 6 patients were not eligible
    • 5 patients were not recruited due to staff shortages
    • 75 due to patient parent or clinician preference

Randomisation rate 233/313 =74%
Reasons For Refusal OF R1

- Shared Care centre not open near patient
- Short dex would be inadequate treatment due to size of mass
- Language barrier - not ethical to obtain consent
- Didn't want to participate without information on outcomes
- Patient wanted standard treatment
- No reason given
- Unhappy with risks in PIS
- Unable to make a decision so soon after diagnosis
- Language barrier
- Parents wanted standard treatment
- No reason given

Parent decision

Clinical decision
# Randomisation rate by site

<table>
<thead>
<tr>
<th>Site</th>
<th>Screened</th>
<th>Refused</th>
<th>Refusal Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberdeen</td>
<td>3</td>
<td>1</td>
<td>33%</td>
</tr>
<tr>
<td>Addenbrooke's</td>
<td>22</td>
<td>3</td>
<td>13%</td>
</tr>
<tr>
<td>Alder Hey</td>
<td>12</td>
<td>4</td>
<td>33%</td>
</tr>
<tr>
<td>Bristol</td>
<td>25</td>
<td>6</td>
<td>24%</td>
</tr>
<tr>
<td>Belfast</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Cardiff</td>
<td>4</td>
<td>2</td>
<td>50%</td>
</tr>
<tr>
<td>Christie</td>
<td>2</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Churchill Hospital, Oxford</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Dublin</td>
<td>2</td>
<td>2</td>
<td>0%</td>
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<tr>
<td>Edinburgh</td>
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<td>5</td>
<td>0%</td>
</tr>
<tr>
<td>Glasgow</td>
<td>19</td>
<td>4</td>
<td>21%</td>
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<td>GOSH</td>
<td>28</td>
<td>9</td>
<td>32%</td>
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<td>Leeds</td>
<td>30</td>
<td>13</td>
<td>43%</td>
</tr>
<tr>
<td>Leicester</td>
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<td>2</td>
<td>33%</td>
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<tr>
<td>Liverpool</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Manchester</td>
<td>17</td>
<td>3</td>
<td>17%</td>
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<td>Newcastle</td>
<td>16</td>
<td>2</td>
<td>12%</td>
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<tr>
<td>North Staffs</td>
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<td>0</td>
<td>0%</td>
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<tr>
<td>Nottingham City</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Queen's Medical Centre, Nottingham</td>
<td>17</td>
<td>6</td>
<td>35%</td>
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<tr>
<td>Royal Hallamshire</td>
<td>2</td>
<td>1</td>
<td>50%</td>
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<tr>
<td>Royal Marsden</td>
<td>6</td>
<td>4</td>
<td>66%</td>
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<tr>
<td>Sheffield</td>
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<tr>
<td>Southampton</td>
<td>19</td>
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<td>10%</td>
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<tr>
<td>St James, Leeds</td>
<td>2</td>
<td>2</td>
<td>0%</td>
</tr>
<tr>
<td>UCLH</td>
<td>1</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>
RECRUITMENT TO R2

• 173 screened for R2 to date
  – 7 ineligible (2 Ph 3 MTX encephalopathy)
  – 48 patients declined
  – 7 unknown
  – 111 patients randomised

Randomisation rate 111/173 = 64%
**Reasons For Refusal of R2**

<table>
<thead>
<tr>
<th>Reason</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logistics of HD MTX</td>
<td>10</td>
<td>48%</td>
</tr>
<tr>
<td>Toxicity of MTX</td>
<td>3</td>
<td>14%</td>
</tr>
<tr>
<td>Parent choice reason not stated</td>
<td>5</td>
<td>23%</td>
</tr>
<tr>
<td>Didn’t want reduced therapy</td>
<td>3</td>
<td>14%</td>
</tr>
</tbody>
</table>
Day 29 MRD results

- 232 patients reported to CRCTU at day 29
  - 33 ‘missing data’
  - 92 MRD Risk (46%)
  - 95 MRD Low Risk (54%)
  - 12 MRD No Result (6%)
    - 2 inadequate at diagnosis
    - 1 inadequate at day 29
    - 6 no targets
    - 3 not to QR (oligoclonal)
    - 2 MRD High Risk Cytogenetics (1%)
  - 0 T-cell patient with MRD ≥ 10% (0%)
Week 14 MRD results

- 62 patients reported to CRCTU at week 14
  - 1 MRD High Risk (2%)
  - 59 MRD Intermediate Risk (94%)
  - 2 MRD No Result (4%)

- 1 inadequate sample
- 1 not to QR
ON GOING ISSUES

- POSCU
- TYA
- Regulatory Load
- Add On Studies
POSCU’s

- All R&D’s at POSCU’s contacted
- Site contract agreement & CV and GCP training by lead clinical and pharmacist
- Site Initiation Teleconference - 28th August
- karen.howe@gosh.nhs.uk
- megan.wight@gosh.nhs.uk
Serious Adverse Events

• Please report within 24 hours of admission

• Proforma for reporting emailed out

• saes.gosh.nhs.net