UKALL14 News from the CTC Trials Team
December 2015

The UKALL14 trial is recruiting very well and we would like to thank you all for your continued efforts.
We have now registered 582 patients and 66 sites have been activated.

This newsletter focuses on the recent amendment: trial protocol (v7.0), patient information sheet (v5.3), consent documents for constitutional DNA studies, new CRFs and lab forms. If you have any questions about any aspect of the amendment, please contact us (ctc.ukall14@ucl.ac.uk).

PROTOCOL v7.0

The main changes in protocol v7.0 are as follows:

- Optional additional sample for constitutional DNA studies
- Clarifications regarding transplant inclusion criteria and transplant conditioning regimens
- Clarification of the timing of asparaginase level samples in patients aged ≥41
- Clarifications about the scheduling of nelarabine and contraindications to nelarabine administration
- Clarification of SAE reporting timeframes during all phases of treatment
- Addition of an AE of special interest for venous thromboembolisms
- Change of contact details for the MRD laboratory

The protocol now allows centres slightly more flexibility over transplant conditioning. Sites are still expected to follow the conditioning regimens outlined in section 7.2.10 of the protocol wherever possible, however it may be possible to give young patients a RIC transplant, or to make changes to the conditioning regimen used if there is a clinical need – **this must be agreed in advance, and on a patient-by-patient basis, by the UKALL14 Transplant Coordinator, David Marks** (contact details at end of newsletter). Please copy UCL CTC into any correspondence.

The TMG's recommendation that nelarabine should not be given until counts recover following phase 2 induction has been formalised in this amendment. It must not be given if the patient has ≥ grade 2 CNS toxicity at the end of phase 2 however.

Because patients aged ≥41 at study entry only get one dose of pegylated asparaginase during phase 1, their asparaginase level samples cannot be taken on the same schedule as younger patients' samples. Whereas samples for younger patients are taken on days 3/4 and 18, for older patients the first sample should be taken on day 18, before starting pegylated asparaginase, and a second sample taken two weeks later on day 32.

The TMG have a particular interest in venous thromboembolisms in this patient group, and up until now thromboembolic events at any point during the trial were supposed to be reported as SAEs. We realise that filling out SAE forms is a big undertaking, so we have now developed a brief CRF for reporting thromboembolic events that occur outside the SAE reporting window – it should be much quicker and easier to complete than an SAE report form!

Please familiarise yourself with all sections of the new protocol (v7.0) as soon as possible, and please do not hesitate to contact us if you have any questions about the protocol. Sites must adhere to the new protocol from the implementation date (14.12.2015) onwards.

PATIENT INFORMATION SHEET v5.3

The main changes in PIS v5.3 are:

- Updated information about the neurological side effects of nelarabine, and their potential severity
- Additional information about chimerism and MRD monitoring following RIC transplant
- Additional detail about consolidation and maintenance

The new PIS should be used to consent all future patients from the implementation date (14.12.2015) onwards. **Because there is new safety information, patients randomised to arm T2 who have not yet completed nelarabine treatment must be re-consented using PIS v5.3**. The CTC team will contact you if any patients are likely to need re-consenting at your site. Please let us know when a patient re-consents, or if they decide they are no longer happy to receive nelarabine.

CONSTITUTIONAL DNA STUDIES

We have agreed to provide samples for a study looking at the non-leukaemic DNA of ALL patients, aimed at better understanding the causes of ALL. We would like as many UKALL14 patients as possible to provide a sample for this study – although this will be optional. In order to minimise the inconvenience to patients, we will try wherever possible to use DNA from a stored sample if the patient was MRD negative. New patients, and patients without a suitable stored sample will be asked to provide a buccal swab for DNA extraction. Sites will be provided with swabs and instructions.

You have been provided with patient information sheets and consent forms for both eventualities. The CTC study team will let you know which information sheet you should use for each of your site's patients. Please let us know if/when patients consent for constitutional DNA studies, or if they do not wish to provide a sample.

DATA RETURNS

We are pleased to report that CRF compliance is now 80% or more for almost every site, and data quality has also greatly improved. Thank you for all for your hard work in clearing data backlogs – please keep up the good work!

The Independent Data Monitoring Committee met to review the trial in October 2015, and while they were pleased with the overall improvement in form returns, they were concerned that oral mucositis daily questionnaire (OMDQ) returns are still worrying low. **It is very important that all patients having myeloablative conditioning and randomised to palifermin (P1/P2 arms) are given the OMDQ forms and fill them every day.** Please remind your team of the importance of these questionnaires and do your best to ensure patients are reminded to complete them each day.

DISCREPANCIES

Please try to resolve data queries by the deadlines set. Print the query report, write your responses directly on the report. Remember that each page must be signed and dated by a member of staff allocated data management duties on the Delegation Log. Please return the wet ink copy to UCL CTC, and retain a copy at site. **There is no need to send updated CRFs unless specifically requested.**

NEW CRFs

We have recently updated the following CRFs:

- **Registration/Randomisation Form v6.0** – updated to collect information about consent for constitutional DNA studies and family history information
- **Adverse Event Form v3.0** – minor corrections
- **Treatment Summary Form v4.0**– removal of 'withdrawal of consent' as a reason for stopping trial treatment early (see also changes to Lost to Follow Up Form)
- **Lost to Follow Up Form v3.0** – clarification regarding patients that choose to stop trial treatment not automatically result in withdrawal from the trial as a whole
- **Death form v3.0** – minor corrections

There are two new CRFs being introduced alongside protocol v7.0:

- **Thromboembolic Event Urgent Event Form v1.0** – this will be used to report venous thromboembolisms (VTEs) occurring outside the SAE reporting windows, and needs to be completed and sent to UCL CTC within 7 calendar days of becoming aware that a VTE has been diagnosed.
- **Informed Consent - Constitutional DNA v1.0** - this will be used to collect information about consent for constitutional DNA studies and family history information for patients registered to UKALL14 prior to the implementation date of Protocol v7.0.

A full list of current CRFs is given below. Remember, the current CRFs are available for download on the CTC website (www.ctc.ucl.ac.uk), so if you aren't sure whether you are using the right versions, please log onto the website at any time and check.

CURRENT CRFs

CRF Name	Current Version (date)	Use From Date
Registration	6.0 (27 Nov 15)	14 Dec 15
Cytogenetics	3.0 (3 May 13)	May 13
Induction Treatment – Phase 1	3.0 (20 Apr 15)	20 Apr 15
Induction Treatment – Phase 2	3.0 (20 Apr 15)	20 Apr 15
Post Induction Treatment Allocation (PITA)	2.0 (20 Apr 15)	20 Apr 15
Post Induction Registration – Maintenance	2.0 (20 Apr 15)	20 Apr 15
Post Induction Registration - Transplant	2.0 (20 Apr 15)	20 Apr 15
Intensification	2.0 (20 Apr 15)	20 Apr 15
Consolidation	2.0 (20 Apr 15)	20 Apr 15
Maintenance	1.0 (8 Dec 10)	Dec 10
Transplant – 9 individual forms	2.0 (20 Apr 15)	20 Apr 15
Treatment Summary	4.0 (27 Nov 15)	14 Dec 15
Annual Follow-up (Not in CR after Phase 2)	2.0 (20 Apr 15)	20 Apr 15
Annual Follow-up (Relapse/Secondary Malignancy)	2.0 (20 Apr 15)	20 Apr 15
Annual Follow-up (Long)	2.0 (20 Apr 15)	20 Apr 15
2 Year Additional Follow-Up	2.0 (20 Apr 15)	20 Apr 15
Relapse	2.0 (19 Apr 11)	Apr 11
Death	3.0 (27 Nov 15)	14 Dec 15
Second Cancer	2.0 (20 Apr 15)	20 Apr 15
Lost to Follow-up	3.0 (27 Nov 15)	14 Dec 15
Centre Transfer	2.0 (19 Apr 11)	Apr 11
Adverse Events – Induction Phase 1	3.0 (27 Nov 15)	14 Dec 15
Adverse Events – Induction Phase 2	3.0 (27 Nov 15)	14 Dec 15
Adverse Events – Intensification	3.0 (27 Nov 15)	14 Dec 15
Adverse Events – Consolidation	3.0 (27 Nov 15)	14 Dec 15
Adverse Events – Transplant	3.0 (27 Nov 15)	14 Dec 15
Adverse Event of Special Interest	1.0 (27 Nov 15)	14 Dec 15
Informed Consent for Constitutional DNA	1.0 (27 Nov 15)	14 Dec 15

CURRENT DOCUMENTS

Document name	Version number	Version date
Protocol	7.0	09 Sep 2015
Patient Information Sheet	5.3	09 Sep 2015
Consent Form	1.2	29 Apr 2015
Patient Information Sheet – Additional Genetic Testing (stored BM)	1.0	09 Sep 2015
Patient Information Sheet – Additional Genetic Testing (buccal swab)	1.0	09 Sep 2015
Consent Form – Additional Genetic Testing (stored BM)	1.0	09 Sep 2015
Consent Form – Additional Genetic Testing (buccal swab)	1.0	09 Sep 2015
Pregnancy Monitoring Information Sheet (Patient)	1.0	01 Aug 2012
Pregnancy Monitoring Information Sheet (Partner)	1.0	01 Aug 2012
Pregnancy Monitoring Consent Form (Patient)	1.0	01 Aug 2012
Pregnancy Monitoring Consent Form (Partner)	1.0	01 Aug 2012
GP letter	1.0	11 Nov 2009
Patient card	1.0	11 Nov 2009
Sample Request Form	3.0	09 Nov 2015

UPDATED SAMPLE REQUEST FORM

As you know, the MRD laboratory has recently moved to UCL Cancer Institute, however the chimerism laboratory is still at the Royal Free Hospital, the pre- and post-transplant MRD and chimerism samples now have to be sent to different addresses. **Sample request form v3.0** has recently been released, and includes the addresses for each laboratory. Please make sure you use the correct address, otherwise there will be a delay in processing them and they may not be usable.

CHRISTMAS CLOSURE DATES

Please see the calendar below outlining the closure dates and cover for these dates at UCL CTC.

Monday	Tuesday	Wednesday	Thursday	Friday
21st December Normal Operation 09:00-17:00	22nd December Normal Operation 09:00-17:00	23rd December Normal Operation 09:00-17:00	24th December Open - limited cover 10:00-16:00	25th December CLOSED
28th December CLOSED	29th December Open - limited cover 10:00-16:00	30th December Open - limited cover 10:00-16:00	31st December Open - limited cover 10:00-16:00	1st January CLOSED

We will send details of the drug ordering arrangements and lab arrangements for the Christmas period shortly.

THANK YOU

We hope that this newsletter helps to clarify any new and uncertain areas, and look forward to continuing our collaborative efforts with all participating sites to ensure the ongoing success of the UKALL14 trial.

TRIAL CONTACTS

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