



## Clinical trial results:

**Randomised controlled open-label trial of TPF induction chemotherapy in the surgical management of locally advanced head and neck cancer (T = taxane, P = cisplatin, F = 5-fluorouracil)**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-023195-22 |
| Trial protocol           | GB             |
| Global end of trial date | 05 May 2020    |

### Results information

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)  |
| This version publication date     | 23 May 2020   |
| First version publication date    | 23 May 2020   |
| Summary attachment (see zip file) | TITAN Final Statistical Report (TITAN final statistical report _ Version 1 05May2020.pdf) |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | UoL000501 |
|-----------------------|-----------|

#### Additional study identifiers

|                                    |  |
|------------------------------------|--|
| ISRCTN number                      | ISRCTN74465582   |
| ClinicalTrials.gov id (NCT number) | -  |
| WHO universal trial number (UTN)   | -  |
| Other trial identifiers            | Aintree University Hospital NHS Trust Reference: 391/11, REF Reference: 11/NW/0149 |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | The University of Liverpool,   |
| Sponsor organisation address | 3 Brownlow Street, Liverpool, United Kingdom, L69 3GI  |
| Public contact               | Mr Alex Astor, University of Liverpool - Research Support Office<br>, 0044 1517948739, sponsor@liverpool.ac.uk   |
| Scientific contact           | Mr Alex Astor, University of Liverpool - Research Support Office<br>, 0044 1517948739, sponsor@liverpool.ac.uk   |
| Sponsor organisation name    | Aintree University Hospitals NHS Foundation Trust  |
| Sponsor organisation address | Longmoor Lane , Liverpool, United Kingdom, L9 7AL  |
| Public contact               | Mrs Michelle Mossa -, Aintree University Hospitals NHS Foundation Trust - Research and Development Department, 0044 151 5295924, MICHELLE.MOSSA@aintree.nhs.uk |
| Scientific contact           | Mrs Michelle Mossa -, Aintree University Hospitals NHS Foundation Trust - Research and Development Department, 0044 151 5295924, MICHELLE.MOSSA@aintree.nhs.uk |

Notes:

---

## Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

---

## Results analysis stage

|  |             |
|--|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 05 May 2020 |
| Is this the analysis of the primary completion data? | No          |

|                                  |             |
|----------------------------------|-------------|
| Global end of trial reached?     | Yes         |
| Global end of trial date         | 05 May 2020 |
| Was the trial ended prematurely? | Yes         |

Notes:

---

## General information about the trial

Main objective of the trial:

The primary aim is to determine whether enough patients agree to be randomised in this feasibility study so that the full phase III would be able to recruit the target sample size within 4 more years. This will be determined by setting up at least 4 centres, each of which should recruit an average of 1 patient per month during a 12 month period.

Primary Objective: Rate of recruitment into the TITAN trial over a period of 12 months from at least 4 centres

Secondary Objectives: 1. Randomisation: Screening Ratio 2. The percentage of patients in the TPF arm who complete the full course of treatment (including post-operative radiotherapy / chemoradiotherapy)

Protection of trial subjects:

Informed Consent: Subjects will only be eligible to enter the study if they have provided written informed consent, following information provided by the research team and have been given the opportunity to discuss the study with the Principal Investigator.

Timing of consent process (e.g. limited time for trials in emergency care): It was requested that the recruiting centre did not recruit patients to TITAN on the same day as their cancer diagnosis was confirmed, and certainly not on the day that treatment is due to commence. A minimum time of 24 hours was implemented before consenting to the trial.

Any additional visits and/or tests required by the trial: Other than the possibility of an extra appointment to discuss recruitment to the trial, and attendance at a PETCT scan those in the standard treatment arm will not have to attend additional appointments.

Follow-up: Follow-up appointments will be largely contained within the routine clinical follow up of such patients.

---

Background therapy:

None

---

Evidence for comparator:

Induction chemotherapy is a significant recent advance in the management of locally advanced SCCHN and its use in combination with surgery and postoperative radiotherapy has been widely suggested in this setting. The proponents of induction chemotherapy reasonably argue that it allows better delivery of drugs to "treatment naïve" tumours with an intact blood supply and at the same time provides maximal treatment to eradicate micrometastasis. It is anticipated that control of both local recurrence as well as regional and distant relapse might reasonably be expected to be improved by the addition of the very active drug docetaxel. Some of the potential improvements could theoretically be obtainable by using these drugs in the postoperative setting. However in reality the acute and long term toxicity of combining chemotherapy with radiotherapy following major head and neck surgery is greatly limiting in

achieving the required dose intensity of the critical agents. By exploiting this most effective therapy in a neoadjuvant setting it is hoped that the balance between overall survival (OS) and functional outcome can genuinely be advanced in these most challenging cases with locally advanced disease.

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 02 November 2011 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United Kingdom: 7 |
| Worldwide total number of subjects   | 7                 |
| EEA total number of subjects         | 7                 |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |
| Adolescents (12-17 years)                 | 0 |
| Adults (18-64 years)                      | 5 |
| From 65 to 84 years                       | 2 |
| 85 years and over                         | 0 |

## Subject disposition

### Recruitment

Recruitment details:

11 sites were open to recruitment, however only 6 sites managed to screen at least 1 patient. Patients were randomised from just 3 tertiary NHS sites across the UK.

The first patient was randomized on 15/08/2012 and the last on 04/02/2013.

The study was terminated early by the ISDMC due to poor recruitment and lack of feasibility.

### Pre-assignment

Screening details:

Patients eligible for the TITAN trial were screened through the H&N MDT completed up to 28 days before randomisation.

Procedures include:

Clinical examination

Radiological imaging of H&N

Detailed medical history

Final pathological report on diagnostic biopsy (i.e. fixed tissue, H&E )

MDT decision for primary surgery

PET/CT

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

Blinding implementation details:

n/a - Study open label

### Arms

|                              |                              |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes                          |
| Arm title                    | Induction chemotherapy (ICT) |

Arm description:

Induction chemotherapy (ICT): Docetaxel, Cisplatin, 5-Fluorouracil Agent / (5-FU) x 3 Cycles

The TPF induction chemotherapy regimen for this study consists three cycles of the following at 21 day intervals:

Docetaxel 75mg/m<sup>2</sup> day 1

Cisplatin 75mg/m<sup>2</sup> day 1

5-Fluorouracil 750mg/m<sup>2</sup>/on day 1, day 2, day 3 and day-4 (total dose 3000mg/m<sup>2</sup>)

|  |   |
|--|---|
| Arm type                               | Experimental                                      |
| Investigational medicinal product name | Taxotere  |
| Investigational medicinal product code | L01CD02   |
| Other name                             | Doxcetaxol  |
| Pharmaceutical forms                   | Concentrate and solvent for solution for infusion |
| Routes of administration               | Intravenous use                                   |

Dosage and administration details:

Patients received 75mg/m<sup>2</sup> per cycle for 3 cycles at 21 day intervals

|  |   |
|--|---|
| Investigational medicinal product name | Cisplatin   |
| Investigational medicinal product code | L01XA01   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                       |

Dosage and administration details:

Patients received 75mg/m<sup>2</sup> per cycle for 3 cycles at 21 day intervals

|   |                                       |
|---|---------------------------------------|
| Investigational medicinal product name                                  | Fluorouracil                          |
| Investigational medicinal product code                                  | L01BC02                               |
| Other name  |                                       |
| Pharmaceutical forms  | Concentrate for solution for infusion |
| Routes of administration  | Intravenous use                       |
| Dosage and administration details:                                      |                                       |
| Patients received 750mg/m2 per cycle for 3 cycles at 21 day intervals   |                                       |
| <b>Arm title</b>  | Surgery                               |
| Arm description:  |                                       |
| Conventional surgical resection carried out with 10mm clinical margins. |                                       |
| Arm type  | Standard of Care                      |
| No investigational medicinal product assigned in this arm               |                                       |

| <b>Number of subjects in period 1</b> | Induction chemotherapy (ICT) | Surgery |
|---------------------------------------|------------------------------|---------|
| Started                               | 3                            | 4       |
| Completed                             | 1                            | 2       |
| Not completed                         | 2                            | 2       |
| Lost to follow-up                     | 2                            | 2       |

## Baseline characteristics

### Reporting groups

|   |                              |
|---|------------------------------|
| Reporting group title   | Induction chemotherapy (ICT) |
| Reporting group description:  |                              |
| Induction chemotherapy (ICT): Docetaxel, Cisplatin, 5-Fluorouracil Agent / (5-FU) x 3 Cycles                      |                              |
| The TPF induction chemotherapy regimen for this study consists three cycles of the following at 21 day intervals: |                              |
| Docetaxel 75mg/m2 day 1   |                              |
| Cisplatin 75mg/m2 day 1   |                              |
| 5-Fluorouracil 750mg/m2/on day 1, day 2, day 3 and day-4 (total dose 3000mg/m2)                                   |                              |
| Reporting group title   | Surgery                      |
| Reporting group description:  |                              |
| Conventional surgical resection carried out with 10mm clinical margins.   |                              |

| Reporting group values                             | Induction chemotherapy (ICT) | Surgery | Total |
|--|------------------------------|---------|-------|
| Number of subjects                                 | 3                            | 4       | 7     |
| Age categorical                                    |                              |         |       |
| Age in years                                       |                              |         |       |
| Units: Subjects                                    |                              |         |       |
| In utero   | 0                            | 0       | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                            | 0       | 0     |
| Newborns (0-27 days)                               | 0                            | 0       | 0     |
| Infants and toddlers (28 days-23 months)           | 0                            | 0       | 0     |
| Children (2-11 years)                              | 0                            | 0       | 0     |
| Adolescents (12-17 years)                          | 0                            | 0       | 0     |
| Adults (18-64 years)                               | 2                            | 3       | 5     |
| From 65-84 years                                   | 1                            | 1       | 2     |
| 85 years and over                                  | 0                            | 0       | 0     |
| Age continuous                                     |                              |         |       |
| Age  |                              |         |       |
| Units: years                                       |                              |         |       |
| arithmetic mean                                    | 60.9                         | 61.8    |       |
| standard deviation                                 | ± 5.1                        | ± 4.4   | -     |
| Gender categorical                                 |                              |         |       |
| Units: Subjects                                    |                              |         |       |
| Female   | 1                            | 1       | 2     |
| Male   | 2                            | 3       | 5     |
| WHO status   |                              |         |       |
| Units: Subjects                                    |                              |         |       |
| WHO status 0                                       | 1                            | 3       | 4     |
| WHO status 1                                       | 2                            | 1       | 3     |
| Ethnicity  |                              |         |       |
| Units: Subjects                                    |                              |         |       |
| White - British                                    | 3                            | 4       | 7     |
| Smoking status                                     |                              |         |       |
| Units: Subjects                                    |                              |         |       |
| Never smoked                                       | 1                            | 1       | 2     |

|   |       |        |   |
|---|-------|--------|---|
| Ex-smoker   | 0     | 2      | 2 |
| Current smoker  | 2     | 1      | 3 |
| Alcohol status  |       |        |   |
| Units: Subjects   |       |        |   |
| None  | 1     | 0      | 1 |
| Sporadic  | 1     | 2      | 3 |
| Regular   | 1     | 2      | 3 |
| HIS Stage   |       |        |   |
| HIS Stage prior to treatment                            |       |        |   |
| Units: Subjects   |       |        |   |
| HIS stage 3   | 0     | 1      | 1 |
| HIS stage 4   | 3     | 3      | 6 |
| Diagnosis of squamous cell carcinoma                    |       |        |   |
| Diagnosis of squamous cell carcinoma prior to treatment |       |        |   |
| Units: Subjects   |       |        |   |
| No  | 1     | 0      | 1 |
| Yes   | 1     | 2      | 3 |
| Missing   | 1     | 2      | 3 |
| TNM Staging - T stage                                   |       |        |   |
| TNM staging - T stage prior to treatment                |       |        |   |
| Units: Subjects   |       |        |   |
| T stage 04  | 2     | 2      | 4 |
| T stage missing   | 1     | 2      | 3 |
| TNM Staging - N stage                                   |       |        |   |
| TNM staging - N stage prior to treatment                |       |        |   |
| Units: Subjects   |       |        |   |
| N stage 00  | 0     | 1      | 1 |
| N stage 01  | 1     | 0      | 1 |
| N stage 02  | 1     | 1      | 2 |
| N stage missing   | 1     | 2      | 3 |
| TNM Staging - M stage                                   |       |        |   |
| TNM staging - M stage prior to treatment                |       |        |   |
| Units: Subjects   |       |        |   |
| M stage 00  | 2     | 1      | 3 |
| M stage missing   | 1     | 3      | 4 |
| ECG   |       |        |   |
| ECG prior to treatment                                  |       |        |   |
| Units: Subjects   |       |        |   |
| Normal  | 2     | 2      | 4 |
| Missing   | 1     | 2      | 3 |
| Height  |       |        |   |
| Units: cm   |       |        |   |
| arithmetic mean   | 179.7 | 176.1  |   |
| standard deviation                                      | ± 7.6 | ± 10.5 | - |
| Weight  |       |        |   |
| Units: kg   |       |        |   |
| arithmetic mean   | 70.8  | 73.0   |   |
| standard deviation                                      | ± 9.6 | ± 23.7 | - |

## End points

### End points reporting groups

|  |                              |
|--|------------------------------|
| Reporting group title  | Induction chemotherapy (ICT) |
| Reporting group description:<br>Induction chemotherapy (ICT): Docetaxel, Cisplatin, 5-Fluorouracil Agent / (5-FU) x 3 Cycles<br>The TPF induction chemotherapy regimen for this study consists three cycles of the following at 21 day intervals:<br>Docetaxel 75mg/m2 day 1<br>Cisplatin 75mg/m2 day 1<br>5-Fluorouracil 750mg/m2/on day 1, day 2, day 3 and day-4 (total dose 3000mg/m2) |                              |
| Reporting group title  | Surgery                      |
| Reporting group description:<br>Conventional surgical resection carried out with 10mm clinical margins.  |                              |

### Primary: Rate of recruitment into TITAN trial over a period of 12 months from at least 4 centres

|                 |  |
|-----------------|--|
| End point title | Rate of recruitment into TITAN trial over a period of 12 months from at least 4 centres <sup>[1]</sup> |
|-----------------|--|

#### End point description:

The rate of recruitment was very slow over the duration of the trial before it was decided by the TSC to close the study to further recruitment on 24 May 2013.

From 02 Nov 2011 to 24 May 2013, the number of recruiting sites who screened at least one patient was 6, however only 3 of these 6 centres randomised patients onto the TITAN study.

Over the 19 months the recruiting sites were open, only 7 patients were randomised onto the study.

No statistical analysis was planned or has been conducted for this primary end point.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

#### End point timeframe:

Rate of recruitment into the TITAN trial over a period of 12 months from at least 4 centres

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the primary end point was rate of recruitment into the TITAN trial over a period of 12 months from at least 4 centres, no statistical analysis was planned or has been conducted for this primary end point.

| End point values            | Induction chemotherapy (ICT) | Surgery          |  |  |
|-----------------------------|------------------------------|------------------|--|--|
| Subject group type          | Reporting group              | Reporting group  |  |  |
| Number of subjects analysed | 3 <sup>[2]</sup>             | 4 <sup>[3]</sup> |  |  |
| Units: subjects             | 3                            | 4                |  |  |

#### Notes:

[2] - The primary end point is not analysed by treatment group as measuring rate of recruitment overall

[3] - Primary end point is not analysed by treatment group as measuring recruitment rate overall

### Statistical analyses

No statistical analyses for this end point

### Secondary: Randomisation : Screening ratio



|  |                                 |
|--|---------------------------------|
| End point title  | Randomisation : Screening ratio |
| End point description:   |                                 |
| In order for the 7 patients to be randomised into the TITAN trial, a total of 85 patients were screened by 6 active recruiting centres (11 recruiting sites were open in total).   |                                 |
| Over the 19 month recruiting period, before the trial was closed early, this equates to a randomisation : screening ratio of 7 : 85 (i.e. 1 : 12.1 ratio).   |                                 |
| Based on this randomisation : screening ratio and rate of recruitment, a total of 605 patients would have needed to be screened over a period of 85 months to randomised the originally planned 50 patients for the TITAN trial. |                                 |
| End point type   | Secondary                       |
| End point timeframe:   |                                 |
| Due to very slow recruitment, the initial recruitment period was extended. There was a 19 month recruiting period from 02 Nov 2011 to 24 May 2013 (date when TSC closed study to further recruitment).                           |                                 |

| End point values            | Induction chemotherapy (ICT) | Surgery          |  |  |
|-----------------------------|------------------------------|------------------|--|--|
| Subject group type          | Reporting group              | Reporting group  |  |  |
| Number of subjects analysed | 3 <sup>[4]</sup>             | 4 <sup>[5]</sup> |  |  |
| Units: Subjects             | 3                            | 4                |  |  |

Notes:

[4] - The secondary end point is not analysed by treatment group as randomisation:screening ratio overall

[5] - The secondary end point is not analysed by treatment group as randomisation:screening ratio overall

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of patients in the Induction Chemotherapy (ICT) arm who complete the full course of treatment (including post-operative radiotherapy (PORT) / chemo-radiotherapy (CRT))

|                 |   |
|-----------------|---|
| End point title | Percentage of patients in the Induction Chemotherapy (ICT) arm who complete the full course of treatment (including post-operative radiotherapy (PORT) / chemo-radiotherapy (CRT)) <sup>[6]</sup> |
|-----------------|---|

End point description:

Of the 7 patients randomised, 3 patients were randomised to the TPF induction chemotherapy arm.

Of these 3 patients, only 1 patient received the 3 cycles of TPF induction chemotherapy. Having completed the 3 cycles, the patient was assessed and also re-assessed for surgery on the primary tumour site and neck(s). However, the CRF records received show that this patient did not go on to receive their surgery before the trial discontinued prematurely. Thus they could not then be assessed to receive the post-operative radiotherapy (PORT) or chemo-radiotherapy (CRT).

The other 2 randomised patients do not appear to have received any TPF induction chemotherapy and subsequently no surgery of POST / CRT.

During the 19 month duration of the trial, before being terminated due to poor recruitment, no patients in the TPF arm completed the full course of treatment (including post-operative radiotherapy / chemo-radiotherapy).

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Following randomisation, baseline measures (prior to treatment). As minimum criteria, within 28 days of commencing definitive therapy. Then 3 cycles of TPF induction chemotherapy, followed by surgery to |           |

primary site and neck(s) and then PORT or CRT.

---

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This secondary endpoint was pre-planned to focus purely on the percentage of patients in the experimental arm (i.e. induction chemotherapy (ICT) arm) who complete the full course of treatment.

No comparison of the percentage of patients who complete the full course of treatment was pre-planned between the standard of care arm and the experimental arm (i.e. induction chemotherapy).

| <b>End point values</b>     | Induction chemotherapy (ICT) |  |  |  |
|-----------------------------|------------------------------|--|--|--|
| Subject group type          | Reporting group              |  |  |  |
| Number of subjects analysed | 3                            |  |  |  |
| Units: Subjects             | 3                            |  |  |  |

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events should be reported from the point of consent until 28 days post completion of all primary treatment (post-operative radio or chemoradiotherapy).

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |           |
|-----------------|-----------|
| Dictionary name | NCI CTCAE |
|-----------------|-----------|

|                    |     |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

### Reporting groups

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Induction chemotherapy (ICT) arm |
|-----------------------|----------------------------------|

Reporting group description: -

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Surgery (Standard of Care) arm |
|-----------------------|--------------------------------|

Reporting group description: -

| <b>Serious adverse events</b>                     | Induction chemotherapy (ICT) arm | Surgery (Standard of Care) arm |  |
|---|----------------------------------|--------------------------------|--|
| Total subjects affected by serious adverse events |                                  |                                |  |
| subjects affected / exposed                       | 0 / 3 (0.00%)                    | 0 / 4 (0.00%)                  |  |
| number of deaths (all causes)                     | 0                                | 0                              |  |
| number of deaths resulting from adverse events    | 0                                | 0                              |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                     | Induction chemotherapy (ICT) arm  | Surgery (Standard of Care) arm |  |
|---|---|--------------------------------|--|
| Total subjects affected by non-serious adverse events |   |                                |  |
| subjects affected / exposed                           | 1 / 3 (33.33%)  | 2 / 4 (50.00%)                 |  |
| Surgical and medical procedures                       |   |                                |  |
| Other   | Additional description: Patient 1: Exposed bone between lower lip and chin 3-4mm.<br>Patient 2: Exposed plate right lateral aspect of mental sub unit; hospital acquired pneumonia; infection around tracheostomy site; infection left side of chin |                                |  |
| subjects affected / exposed                           | 0 / 3 (0.00%)   | 2 / 4 (50.00%)                 |  |
| occurrences (all)                                     | 0   | 5                              |  |
| Ear and labyrinth disorders                           |   |                                |  |
| Tinnitus  |   |                                |  |
| subjects affected / exposed                           | 1 / 3 (33.33%)  | 0 / 4 (0.00%)                  |  |
| occurrences (all)                                     | 1   | 0                              |  |

|  |                     |                    |  |
|--|---------------------|--------------------|--|
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | 0 / 4 (0.00%)<br>0 |  |
|--|---------------------|--------------------|--|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 11 August 2011  | <ol style="list-style-type: none"><li>1. The labels need to be updated as it contains the old LCTU address. The sponsor's pharmacist has indicated that this is changed to Aintree's address.</li><li>2. Some small typing errors have been noted with the protocol. This includes:<ol style="list-style-type: none"><li>a. P28 Section 7.2.4.2 – The protocol has been updated to specify Cisplatin as the post-operative radiotherapy</li><li>b. P28 Section 7.2.4.2 – Carboplatin AUC 5mg/ml/mon should read Carboplatin AUC5</li><li>c. Appendix N – Example labels to be removed.</li><li>d. Section 7.3.1 – Section Updated to indicate the labelling should be towards Annex 13, rather than refer to Appendix N.</li></ol></li></ol>   |
| 19 October 2011 | <ol style="list-style-type: none"><li>1. NIHR Radiotherapy Trials Quality Assurance group requested that the anonymised radiotherapy plans are shared with them, so they can obtain an overview of all RT research being conducted</li><li>2. In the IRAS form, it has been documented that exposure to radiotherapy does not exceed that of standard care. This was queried by one of the sites, as they indicated that at least one of the PET scans is extra to standard care. It was conceded that although minimal, the exposure to radiation is above that of standard care.</li><li>3. It has been documented in the CTA, that the IMP is Taxotere; this is a brand of Docetaxel. The IMP should be listed as Docetaxel; this will allow sites to use any generic approved brand of Docetaxel.</li><li>4. The total dose of Fluorouracil is listed as 2250mg/m<sup>2</sup>. However, this should be listed as 9000mg/m<sup>2</sup>. As the total dose allowed per cycle is 3000mg/m<sup>2</sup>, across the three cycles this would be 9000mg/m<sup>2</sup>.</li><li>5. Changes to Safety Events Reporting Procedure - Protocol Section 13.8 - Adverse Event reporting Procedures has been revised to reflect the introduction of remote data entry for adverse event reporting within the LCTU. The original protocol required SAEs and AEs to be reported within the regulatory timelines to the LCTU via fax. This has been updated as a new system allowing research staff to enter data on line has been implemented for this trial.</li><li>6. Changes to the screening procedure. Protocol Section 6.1 indicates that screening will be performed upon a patient's possible eligibility for the study as above and must be documented on the "Screening and Enrolment log". The protocol will be clarified to confirm that the screening and enrolment log will be held electronically.</li><li>7. ISCRTN has been allocated, and will be updated in the protocol.</li></ol> |
| 11 May 2012     | <p>The protocol (Version 4, 05 Sept 11) requires that GFR is completed at a number of timepoints during the trial. In Appendix B of the protocol, it states that an option for the GFR is to use 51-Cr labelled EDTA. During review of the study by one of the sites, it was noted that this assessment was omitted, in error, from the ionising radiation section of the IRAS form.</p> <p>After discussing the omission with Phillip Mayles, the medical physics expert, it was recommended that the ionising radiation section on the IRAS form was updated to include the assessment</p>   |

|              |  |
|--------------|--|
| 26 July 2012 | <p>Protocol Amendment:</p> <p>Protocol Appendix F &amp; Section 8.5: The protocol has been updated to reflect the the PET_CT aspect of the protocol, is optional, for these centres who are struggling obtain NHS funding for these assessment.</p> <p>Protocol Appendix F &amp; Section 8.5: Updates have been made to the scanning protocol of the PET scans to reflect current best practice.</p> <p>Protocol Section 7.2.4.2: To allow sites to follow their own practice, the protocol has been updated to allow sites to use their local AUC practise with regards to Carboplatin</p> <p>Protocol Section 10: Following a procedural change in at the LCTU, a minor change has been made to the pharmacovigilance section, to indicate that the site should always received an acknowledgement when the SAE is reported, and what to of if the electronic reporting system is down.</p> <p>Protocol Section 8: The schedule of assessment will be updated to extend the timeline PET scans to baseline. It is a restriction on recruitment to ensure that this is done before randomisation, especially since it is only necessary to ensure that the PET scan is completed prior to treatment. Distant Metastases may be ruled out using conventional imaging methods</p> |
|--------------|--|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date        | Interruption  | Restart date |
|-------------|---|--------------|
| 24 May 2013 | It was decided by the TSC to close this study to further recruitment on 24 May 2013 due to the extremely slow and poor rate of recruitment observed over the 19 month duration of the trial, compared to the planned rate of recruitment. | -            |

Notes:

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The results presented in this document represent the data available, at the time of premature discontinuation of the trial, for the phase II feasibility study endpoints that were collected for the very limited number of randomised patients.

Notes: