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 3Gl
Public contact	Mr Alex Astor, University of Liverpool - Research Support Office , 0044 1517948739, sponsor@liverpool.ac.uk
Scientific contact	Mr Alex Astor, University of Liverpool - Research Support Office , 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 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 therequired 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/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)

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/m2 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/m2 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

Arm title	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

Number of subjects in period 1	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:

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.

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[1]

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[2]	4[3]		
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[4]	4[5]		
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))[6]

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).

End point values	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: -

Serious adverse events	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 %

Non-serious adverse events	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. 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 Urinary tract infection subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2011	1. The labels need to updated as it contains the old LCTU address. The sponsor's pharmacist has indicated that this is changed to Aintree's address. 2. Some small typing errors have been noted with the protocol. This includes: a. P28 Section 7.2.4.2 – The protocol has been updated to specify Cisplatin as the post-operative radiotherapy b. P28 Section 7.2.4.2 – Carboplatio AUC 5mg/ml/mon should read Carboplatin AUC5 c. Appendix N – Example labels to be removed. d. Section 7.3.1 – Section Updated to indicate the labelling should be towards Annex 13, rather than refer to Appendix N.
19 October 2011	1. NIHR Radiotherapy Trails 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 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. 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. 4. The total dose of Fluorouracil is listed as 2250mg/m2. However, this should be listed as 9000mg/m2. As the total dose allowed per cycle is 3000mg/m2, across the three cycles this would be 9000mg/m2. 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 reporting 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. 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. 7. ISCRTN has been allocated, and will be updated in the protocol.
11 May 2012	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. 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

26 July 2012	Protocol Amendment: Protocol Appendix F & 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. Protocol Appendix F & Section 8.5: Updates have been made to the scanning protocol of the PET scans to reflect current best practice. 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 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. 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

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: