

**Clinical trial results:****A Phase II Trial of docetaxel, cisplatin and 5FU chemotherapy in locally advanced and metastatic carcinoma of the penis****Summary**

EudraCT number	2008-000707-28
Trial protocol	GB
Global end of trial date	27 September 2017

Results information

Result version number	v1 (current)
This version publication date	12 October 2018
First version publication date	12 October 2018

Trial information**Trial identification**

Sponsor protocol code	ICR-CTSU/2008/10016
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Additional study identifiers

ISRCTN number	ISRCTN78108737
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor ID number: CCR3071, CRUK reference number: CRUK/09/001, Main REC Reference Number: 08/H0718/78, MHRA CTA number: 22138/0011/001-0001

Notes:

Sponsors

Sponsor organisation name	The Institute of Cancer Research
Sponsor organisation address	15 Cotswold Road, Sutton, United Kingdom, SM2 5NG
Public contact	Penile TPF Clinical Trials Programme Manager, The Institute of Cancer Research, 0208 7224261, peniletpf-icrctsu@icr.ac.uk
Scientific contact	Penile TPF Clinical Trials Programme Manager, The Institute of Cancer Research, 0208 7224261, peniletpf-icrctsu@icr.ac.uk
Sponsor organisation name	University Hospitals Bristol NHS Foundation Trust
Sponsor organisation address	Education Centre, Level 3, Upper Maudlin Street, Bristol, United Kingdom, BS2 8AE
Public contact	Diana Benton, University Hospitals Bristol NHS Foundation Trust, 0117 342 0227, Diana.Benton@UHBristol.nhs.uk
Scientific contact	Diana Benton, University Hospitals Bristol NHS Foundation Trust, 0117 342 0227, Diana.Benton@UHBristol.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	21 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2017
Global end of trial reached?	Yes
Global end of trial date	27 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the activity of combination docetaxel, cisplatin and 5FU (TPF) chemotherapy in cancer of the penis and thus determine whether this regimen warrants further research.

Protection of trial subjects:

For trial entry and optional tissue donation, patients were given a verbal explanation, discussion and written information. The Principal Investigator at each site was responsible for ensuring written informed consent was obtained for each patients.

Eligible patients were given as much time as they needed to consider and come to a decision about entering the trial, prior to giving consent for registration. The patient information sheet, described fully which parties would have access to their identifiable personal information and patients were asked to give consent to this.

Primary prophylaxis using G-CSF was recommended prior to commencing trial treatment, by the Trial Management Group. Prophylactic use of G-CSF in subsequent cycles was encouraged in patients who had an episode of neutropenic sepsis.

The trial was overseen by an Independent Data Monitoring Committee, who reviewed the accumulating trial data and could recommend stopping the trial if there was any cause for concern about patient safety and if this were the case the patient's oncologist would be notified.

Background therapy: -

Evidence for comparator:

The combination of cisplatin and 5-fluorouracil (PF) has been used to treat advanced squamous carcinoma of the penis since 1990 and is widely regarded as the standard of care in this setting. Three single-institution case series define its activity in a total of 19 patients, with a pooled response rate of 63% (three complete remissions and nine partial remissions) (Fisher et al, 1990; Hussein et al, 1990; Shammas et al, 1992). A retrospective series by Di Lorenzo et al (2012) suggested a response rate of 32% for this regimen, which is more in keeping with anecdotal experience.

The first report of a platinum-taxane combination in penis cancer describes a single patient with locally advanced disease who received carboplatin and paclitaxel (Joerger et al, 2004) and was rendered operable. Subsequent papers have described the use of the TIP regimen (cisplatin, paclitaxel and ifosfamide) in the neoadjuvant setting, confirming its ability to downstage locally advanced disease (Bermejo et al, 2007; Pagliaro et al, 2010).

The combination of docetaxel, cisplatin and 5FU (TPF) has produced high-response rates and improved survival outcomes compared with PF in squamous carcinomas of the head and neck (Posner et al, 2007; Vermorken et al, 2007), which shows histological and some clinical similarities to penis cancer. A single-institution retrospective case series describes the use of the TPF combination in six penis cancer patients with nodal disease: five patients responded, three with pathological complete remission (Pizzocaro et al, 2009). One response is described in six patients with metastatic disease and seven responses in 12 patients treated in the neoadjuvant setting, which would suggest an objective response rate of around 44% (Salvioni et al, 2011).

Actual start date of recruitment	27 August 2009
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: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

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)	19
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty-nine patients were recruited from nine UK centres between September 2009 and December 2010;.

Pre-assignment

Screening details:

Patients that met the eligibility criteria were recruited into the study.

Period 1

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

Arms

Arm title	TPF Chemotherapy
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Arm description:

The TPF chemotherapy regimen consists of docetaxel 75mg/m² day 1 + cisplatin 60mg/m² day 1 followed by 5-fluorouracil 750mg/m²/day 1-5 (total dose 3750mg/m²) with a cycle of 21 days, three cycles to be given in total

Arm type	Experimental
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	L01CD 02
Other name	Taxotere
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

docetaxel 75mg/m² day 1 for 3 cycles

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

Dosage and administration details:

60mg/m² day 1, 3 cycles

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

750mg/m²/day days 1-5, 3 cycles

Number of subjects in period 1	TPF Chemotherapy
Started	29
Completed	21
Not completed	8
patient decision	2
Lack of efficacy	6

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial (overall period)
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Reporting group description: -

Reporting group values	Overall Trial (overall period)	Total	
Number of subjects	29	29	
Age categorical			
Age at registration.			
Units: Subjects			
Adults (18-64 years)	19	19	
From 65-84 years	10	10	
Gender categorical			
Units: Subjects			
Male	29	29	

Subject analysis sets

Subject analysis set title	Evaluable population
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

This population contains all registered patients for whom the primary endpoint can be evaluated.

Patients are excluded from this population if

- o they have died or withdrawn from study treatment prior to completion of 1 cycle (i.e. prior to day 22 of cycle 1), not because of toxicity, or

- o if they have no end of treatment assessment of measurable disease for one of the following reasons:

- o Withdrawal not due to drug (e.g. toxicity) or disease response

- o Non-treatment-related death from cause other than penile cancer

Subject analysis set title	Safety population/Intention to treat
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Intention to treat (ITT): This population contains all patients registered into the study regardless of what happened after registration.

Safety population: This population contains all registered patients who received at least one dose of study drug.

All patients in the ITT population received at least one dose of study drug, therefore, these 2 populations are the same.

Reporting group values	Evaluable population	Safety population/Intention to treat	
Number of subjects	26	29	
Age categorical			
Age at registration.			
Units: Subjects			
Adults (18-64 years)	17	19	
From 65-84 years	9	10	

Gender categorical			
Units: Subjects			
Male	26	29	

End points

End points reporting groups

Reporting group title	TPF Chemotherapy
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Reporting group description:

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Primary: Objective response rate

End point title	Objective response rate ^[1]
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End point description:

The primary endpoint is overall response rate (complete remission rate + partial remission rate).

Response evaluated according to RECIST v1.1 criteria. The objective response rate for this study is defined as the proportion of patients having achieved partial or complete remission according to RECIST criteria on imaging and or clinical measurements (of skin disease) performed at 4 weeks from the date of commencement of the final cycle of chemotherapy.

End point type	Primary
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End point timeframe:

4 weeks from the date of commencement of the final cycle of chemotherapy

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: This is a single arm study and no comparative analysis was performed, however the system expects at least 2 groups to be identified. All methods and options specified in the analysis section apply to statistical methods and summary measures to report and compare at least 2 independent groups, which is not the case in this single arm trial. There is no way of reporting one-group inference and summary values without triggering an error or reporting inaccurate information.

End point values	TPF Chemotherapy	Evaluable population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	26	26		
Units: Patients				
Complete response	2	2		
Partial response	8	8		

Stable disease	8	8		
Progressive disease	6	6		
Died - disease not assessed	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Patients rendered operable by TPF

End point title	Patients rendered operable by TPF
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End point description:

The proportion of patients inoperable at baseline who receive surgery following treatment is analysed as for the primary endpoint, but using the intention-to-treat population . Patients with missing data are handled by presuming no surgery received.

End point type	Secondary
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End point timeframe:

The number and proportion of patients rendered operable after completion of study treatment .

End point values	TPF Chemotherapy	Safety population/Inte ntion to treat		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20 ^[2]	20 ^[3]		
Units: Patients				
Operable at end, yes	4	4		
Operable at end, no	16	16		

Notes:

[2] - 20/29 patients inoperable at baseline

[3] - 20/29 patients inoperable at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival
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End point description:

Progression free survival will be calculated from the date of study entry until a progression occurs. Progression events are defined as clinically or radiologically documented disease progression, or death from any cause. Patients free from a progression event will be censored on the date of last follow up.

A progression-free survival curve will be generated using the methods of Kaplan and Meier. All patients registered in the study will be included. Median and 1-year PFS rate will be reported with 95% CIs.

Duration of response as measured by Kaplan-Meier at each follow-up, or until progression, will be reported.

End point type	Secondary
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End point timeframe:

Progression free survival at 12 months

End point values	Safety population/Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: percentage progression free				
number (confidence interval 95%)	51.1 (31.8 to 67.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
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End point description:

An overall survival curve will be generated using the methods of Kaplan and Meier. All patients registered in the study will be included. The median overall survival will be reported with 95% CI.

End point type	Secondary
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End point timeframe:

Overall survival is defined as the time from registration until death from any cause. Patients alive at time of analysis or lost to follow-up were censored at date last seen.

End point values	Safety population/Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Years				
median (confidence interval 95%)	1.22 (0.53 to 4.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Late toxicity

End point title	Late toxicity
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End point description:

Maximum toxicity CTCAE grades of all toxicities reported over all assessment time points from follow-up of month 6 and onwards.

End point type	Secondary
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End point timeframe:

Toxicities reported by the safety population post treatment from follow-up month 6 and onwards were analysed.

End point values	Safety population/Intention to treat			
Subject group type	Subject analysis set			
Number of subjects analysed	15 ^[4]			
Units: patients				
Grade 1-2	3			
Grade 3-4	12			

Notes:

[4] - Only 15/29 patients reported toxicity data 6 months onwards

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From trial entry to 30 days after last dose of trial treatment

Adverse event reporting additional description:

AE data for patients who received at least 1 dose of experimental treatment.

The non-serious AE section reports all serious and non-serious AEs reported with CTCAEv4, worst grade 3/4 event per person over all on-treatment visits.

In addition, 3 of 19 (15.8%) patients reported grade 3/4 AEs at 3 months (2 peripheral oedema, 1 hypertension).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14
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Reporting groups

Reporting group title	Safety population
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Reporting group description:

Patients who received at least 1 dose of experimental treatment.

In the non-serious adverse events section we report all serious and non-serious adverse events reported with grade 3 or 4 according to the CTCAE grading, that were present in more than 5% of patients.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 29 (48.28%)		
number of deaths (all causes)	20		
number of deaths resulting from adverse events	0		
Investigations			
Neutrophil count			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Surgical and medical procedures			
Laparotomy			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound treatment			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mucosal inflammation			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Vomiting			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	3 / 29 (10.34%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 29 (100.00%)		
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Febrile neutropenia			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
Leukopenia			
subjects affected / exposed	4 / 29 (13.79%)		
occurrences (all)	4		
Neutropenia			
subjects affected / exposed	13 / 29 (44.83%)		
occurrences (all)	13		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	4 / 29 (13.79%) 4		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Infections and infestations Sepsis subjects affected / exposed occurrences (all)	7 / 29 (24.14%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2009	<p>Amendment to update the Trials Unit contact details, amend the inclusion/exclusion criteria, amend protocol appendix 1 - RECIST criteria in line with the new RECIST guidelines and amend appendix 2 of the protocol - Measurement of GFR. Also to declare additional educational grant from Sanofi-Aventis in the Protocol and PIS.</p> <p>PROTOCOL: Amendment to the inclusion criteria to allow patients whose GFR is 55-60ml/min to contact the trials unit for a decision regarding eligibility from the Chief Investigator and co-Chief Investigator.</p> <p>Inclusion of any N1 patients if MDT opinion is to offer chemotherapy as first line neo-adjuvant therapy.</p> <p>Removal of exclusion criteria:</p> <ul style="list-style-type: none"> • T1 N1 M0 disease • T2 N1 M0 disease <p>to tie in with the new inclusion criteria.</p> <p>Appendix 1 - RECIST Criteria - change to the RECIST measuring requirements following the release of the new RECIST guidelines version 1.1</p> <p>Appendix 2 - Measurement of GFR - change to the requirements for the measurement of GFR, from the minimum of the use of the Cockcroft and Gault formula, to the recommended technique of eGFR using the Modification of Diet in Renal Disease (MDRD) formula. Acceptable alternatives were the Cockcroft and Gault Formula (minimum alternative requirement) and direct measurement using EDTA clearance.</p> <p>Financial Matters - declaration of the education grant from Sanofi-Aventis that is used to fund research costs at the ICR-CTSU in the protocol and patient information sheet.</p>
08 June 2010	<p>Sponsor informed of a change in the study drug supply of Taxotere by Sanofi-Aventis.</p> <p>Sanofi-Aventis wrote to The Institute of Cancer Research as co-sponsor of the Penile TPF clinical trial regarding the impending change to the trials supply of Taxotere. Sanofi-Aventis provided (as per contract) Taxotere 20mg & 80mg in a 2-vial presentation (concentrate and solvent), on a free of charge basis.</p> <p>From 21st June 2010, all re-supply requests and new starter packs for sites were fulfilled with a new Taxotere 1-vial presentation (concentrate only). The 2-vial presentation was no longer available.</p> <p>The CTA XML was updated as follows:</p> <ul style="list-style-type: none"> • IMP number PR1 section D.2.1.1.1 Trade name changed from 'TAXOTERE 20 mg concentrate and solvent for solution for infusion' to 'TAXOTERE 20 mg concentrate for solution for infusion' • IMP number PR2 section D.2.1.1.1 Trade name changed from 'TAXOTERE 80 mg concentrate and solvent for solution for infusion' to 'TAXOTERE 20 mg concentrate for solution for infusion'

15 November 2010	<p>Clarification of the definition of a 'non-evaluable' patients where additional patients will be recruited to replace them stating that 26 'evaluable' patients will be recruited and that 'evaluable' patients are required for the primary endpoint. Change to trial schema to state that 'patients deemed fit to receive chemotherapy' are eligible, with removal of 'as palliative or definitive treatment or as treatment for relapse.'</p> <p>Clarification that WHO performance status is required during follow-up. Removal of pre-registration toxicity assessment as this coincided with the pre-cycle 1 toxicity assessment. Inclusion of the Trial Management Group recommendation for primary prophylaxis using GCSF rather than GCSF being used in accordance with local hospital policy. Confirmation that no dose reductions are permitted for 5-Flourouracil.</p>
30 March 2011	<p>The IDMC for the trial want to ensure that long-term follow-up data are only collected if there is a genuine intention to make use of them, for ethical reasons. As such the trial management group made the decision to only collect overall survival and progression data at 36, 48 and 60 months on trial.</p> <p>Amended any reference to "randomisation/randomising/randomised" to "registration/registering/registered" as this is a non-randomised study. The change to the wording was incorrect in the previous protocol, and has now been amended.</p>
06 June 2011	<p>Change to the definition of the end of trial within the protocol, to clarify that the study end date of the trial for all purposes is the date of last data capture.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24169355>