



Clinical trial results:

A randomised trial to determine the impact of timing of surgery and chemotherapy in newly diagnosed patients with advanced epithelial ovarian, primary peritoneal or fallopian tube carcinoma

Summary

EudraCT number	2007-004429-45
Trial protocol	GB
Global end of trial date	16 October 2014

Results information

Result version number	v1 (current)
This version publication date	09 July 2016
First version publication date	09 July 2016
Summary attachment (see zip file)	Chorus Lancet paper (Kehoe_lancet_2015.pdf) Chorus Lancet paper - Supplementary Appendix (Kehoe_lancet_2015_suppl.pdf)

Trial information

Trial identification

Sponsor protocol code	CHORUS
-----------------------	--------

Additional study identifiers

ISRCTN number	ISRCTN74802813
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MRC Clinical Trials Unit at UCL
Sponsor organisation address	Aviation House, 125 Kingsway, London, United Kingdom, WC2B 6NH
Public contact	General enquiries office, MRC Clinical Trials Unit at UCL, 0044 020 7670 4700, enquiries@ctu.mrc.ac.uk
Scientific contact	General enquiries office, MRC Clinical Trials Unit at UCL, 0044 020 7670 4700, enquiries@ctu.mrc.ac.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	31 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2014
Global end of trial reached?	Yes
Global end of trial date	16 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of neoadjuvant chemotherapy i.e. chemotherapy given before and after primary surgery compared to standard surgery followed by chemotherapy

Protection of trial subjects:

National ethical and regulatory approvals were obtained in the UK and New Zealand, with local approvals obtained at each centre. The IDMC and independent Trial Steering Committees oversaw the running of the trial. All participating centres were public hospitals that regularly undertook treatment of ovarian cancer with multidisciplinary teams that included specialist surgeons, oncologists, and pathologists.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 2004
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: 537
Country: Number of subjects enrolled	New Zealand: 13
Worldwide total number of subjects	550
EEA total number of subjects	537

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)	260
From 65 to 84 years	284

85 years and over	6
-------------------	---

Subject disposition

Recruitment

Recruitment details:

Recruitment ran from 5th March 2004 to 26th August 2010.

Pre-assignment

Screening details:

At screening, all women had a clinical assessment, an imaging test (a CT or MRI scan of the abdomen and pelvis, and a radiograph of the chest), and concentrations of serum tumour markers measured (CA125 and CEA).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Primary surgery

Arm description:

Primary surgery followed by six cycles of chemotherapy.

Arm type	Active comparator
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The recommended treatment doses as defined in the protocol are:

- Single-agent Carboplatin either
 - o Target AUC5 x (51Cr-EDTA clearance + 25)mg or
 - o Target AUC6 x (calculated GFR or 24-hour urinary clearance + 25)mg
- Carboplatin in combination with Paclitaxel
 - o Paclitaxel 175mg/m2
 - o Carboplatin either
 - Target AUC5 x (51Cr-EDTA clearance + 25)mg or
 - Target AUC6 x (calculated GFR or 24-hour urinary clearance + 25)

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The recommended treatment doses as defined in the protocol are:

Carboplatin in combination with Paclitaxel

- o Paclitaxel 175mg/m2
- o Carboplatin either
 - Target AUC5 x (51Cr-EDTA clearance + 25)mg or
 - Target AUC6 x (calculated GFR or 24-hour urinary clearance + 25)

Arm title	Primary chemotherapy
------------------	----------------------

Arm description:

Three cycles of primary chemotherapy, then surgery, followed by three more cycles of completion chemotherapy.

Arm type	Experimental
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The recommended treatment doses as defined in the protocol are:

- Single-agent Carboplatin either
 - o Target AUC5 x (51Cr-EDTA clearance + 25)mg or
 - o Target AUC6 x (calculated GFR or 24-hour urinary clearance + 25)mg
- Carboplatin in combination with Paclitaxel
 - o Paclitaxel 175mg/m²
 - o Carboplatin either
 - Target AUC5 x (51Cr-EDTA clearance + 25)mg or
 - Target AUC6 x (calculated GFR or 24-hour urinary clearance + 25)

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The recommended treatment doses as defined in the protocol are:

Carboplatin in combination with Paclitaxel

- o Paclitaxel 175mg/m²
- o Carboplatin either
 - Target AUC5 x (51Cr-EDTA clearance + 25)mg or
 - Target AUC6 x (calculated GFR or 24-hour urinary clearance + 25)

Number of subjects in period 1	Primary surgery	Primary chemotherapy
Started	276	274
Completed	276	274

Baseline characteristics

Reporting groups

Reporting group title	Primary surgery
-----------------------	-----------------

Reporting group description:

Primary surgery followed by six cycles of chemotherapy.

Reporting group title	Primary chemotherapy
-----------------------	----------------------

Reporting group description:

Three cycles of primary chemotherapy, then surgery, followed by three more cycles of completion chemotherapy.

Reporting group values	Primary surgery	Primary chemotherapy	Total
Number of subjects	276	274	550
Age categorical			
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)	128	132	260
From 65-84 years	145	139	284
85 years and over	3	3	6
Age continuous			
Units: years			
median	66	65	
inter-quartile range (Q1-Q3)	57 to 72	59 to 71	-
Gender categorical			
Units: Subjects			
Female	276	274	550
Male	0	0	0
FIGO stage			
Clinical FIGO stage			
Units: Subjects			
FIGO stage III	206	206	412
FIGO stage IV	70	68	138

End points

End points reporting groups

Reporting group title	Primary surgery
Reporting group description: Primary surgery followed by six cycles of chemotherapy.	
Reporting group title	Primary chemotherapy
Reporting group description: Three cycles of primary chemotherapy, then surgery, followed by three more cycles of completion chemotherapy.	

Primary: Overall survival

End point title	Overall survival
End point description:	
End point type	Primary
End point timeframe: OS at data cut-off of 31st May 2014.	

End point values	Primary surgery	Primary chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276	274		
Units: Months				
median (confidence interval 95%)	22.6 (18.6 to 25.9)	21.4 (21 to 28.7)		

Statistical analyses

Statistical analysis title	Overall survival
Statistical analysis description: Hazard ratio to assess non-inferiority. Upper limit of 90% CI needs to exclude 1.18 to meet pre-specified criteria for non-inferiority.	
Comparison groups	Primary surgery v Primary chemotherapy
Number of subjects included in analysis	550
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	90 %
sides	1-sided
upper limit	0.98

Secondary: Progression Free Survival

End point title	Progression Free Survival
-----------------	---------------------------

End point description:

PFS measured from date of randomisation to date of death or confirmed progression. Patients without a date of death are censored at the date they were last known to be alive and progression free.

End point type	Secondary
----------------	-----------

End point timeframe:

PFS up to data cut-off point of 31st May 2014.

End point values	Primary surgery	Primary chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276	274		
Units: Months				
median (confidence interval 95%)	10.7 (9.7 to 11.9)	12 (10.6 to 13.1)		

Statistical analyses

Statistical analysis title	PFS
----------------------------	-----

Statistical analysis description:

Hazard ratio of PFS.

Comparison groups	Primary surgery v Primary chemotherapy
-------------------	--

Number of subjects included in analysis	550
---	-----

Analysis specification	Pre-specified
------------------------	---------------

Analysis type	superiority
---------------	-------------

Parameter estimate	Hazard ratio (HR)
--------------------	-------------------

Point estimate	0.91
----------------	------

Confidence interval

level	95 %
-------	------

sides	2-sided
-------	---------

lower limit	0.76
-------------	------

upper limit	1.09
-------------	------

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Adverse event reporting was scheduled throughout follow-up, but summaries are focussed on the treatment period due to the scarcity of reporting after that point.

Adverse event reporting additional description:

Specific SAE's are listed if >1% of patients in either arm were affected. All other SAE's are grouped under "Other".

Non-serious adverse events were not routinely reported, other than through chemotherapy toxicity reports, and are not included here.

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

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Primary surgery
-----------------------	-----------------

Reporting group description:

Primary surgery followed by six cycles of chemotherapy.

Reporting group title	Primary chemotherapy
-----------------------	----------------------

Reporting group description:

Three cycles of primary chemotherapy, then surgery, followed by three more cycles of completion chemotherapy.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Non-serious adverse events were not routinely collected, other than reporting through chemotherapy toxicities, and are not included here.

Serious adverse events	Primary surgery	Primary chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	67 / 251 (26.69%)	75 / 253 (29.64%)	
number of deaths (all causes)	231	220	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Other events			
subjects affected / exposed	44 / 251 (17.53%)	45 / 253 (17.79%)	
occurrences causally related to treatment / all	11 / 64	11 / 74	
deaths causally related to treatment / all	1 / 10	0 / 5	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	16 / 251 (6.37%)	22 / 253 (8.70%)	
occurrences causally related to treatment / all	4 / 19	5 / 26	
deaths causally related to treatment / all	0 / 0	1 / 1	
Abdominal pain			

subjects affected / exposed	10 / 251 (3.98%)	9 / 253 (3.56%)	
occurrences causally related to treatment / all	0 / 11	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	7 / 251 (2.79%)	7 / 253 (2.77%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowel obstruction			
subjects affected / exposed	3 / 251 (1.20%)	7 / 253 (2.77%)	
occurrences causally related to treatment / all	0 / 3	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Constipation			
subjects affected / exposed	6 / 251 (2.39%)	9 / 253 (3.56%)	
occurrences causally related to treatment / all	0 / 6	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	8 / 251 (3.19%)	6 / 253 (2.37%)	
occurrences causally related to treatment / all	1 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	4 / 251 (1.59%)	6 / 253 (2.37%)	
occurrences causally related to treatment / all	1 / 5	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 251 (1.20%)	4 / 253 (1.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	4 / 251 (1.59%)	4 / 253 (1.58%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	5 / 251 (1.99%)	5 / 253 (1.98%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shortness of breath			
subjects affected / exposed	7 / 251 (2.79%)	5 / 253 (1.98%)	
occurrences causally related to treatment / all	1 / 7	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	5 / 251 (1.99%)	8 / 253 (3.16%)	
occurrences causally related to treatment / all	0 / 5	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Primary surgery	Primary chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 251 (0.00%)	0 / 253 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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/26002111>