



Clinical trial results:

A randomised Phase II study of two pre-operative chemoradiotherapy regimes (oxaliplatin and capecitabine followed by radiotherapy with either oxaliplatin and capecitabine or paclitaxel and carboplatin) for resectable oesophageal cancer.

Summary

EudraCT number	2012-000640-10
Trial protocol	GB
Global end of trial date	04 September 2019

Results information

Result version number	v1 (current)
This version publication date	18 September 2020
First version publication date	18 September 2020
Summary attachment (see zip file)	European Journal of Cancer manuscript (untitled.pdf)

Trial information

Trial identification

Sponsor protocol code	2012/VCC/0009
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Velindre NHS Trust
Sponsor organisation address	Velindre Hospital, Cardiff, United Kingdom,
Public contact	Ruby Ray, Wales Cancer Trials Unit, 02920 687477, al-mokhtarr@cardiff.ac.uk
Scientific contact	Ruby Ray, Wales Cancer Trials Unit, 02920 687477, al-mokhtarr@cardiff.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	30 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2016
Global end of trial reached?	Yes
Global end of trial date	04 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research question is whether it is effective to treat oesophageal cancer patients eligible to receive chemo-radiotherapy with one of two differing radiosensitizer schedules [carboplatin/paclitaxel and oxaliplatin/capecitabine]. The aim of the trial is to select the most effective regime to take forward into a phase III trial in which pre-operative chemo-radiotherapy will be compared with chemotherapy in patients with locally advanced oesophageal cancer at high risk of R1 disease at surgery.

Protection of trial subjects:

The IDMC reviewed the interim data approximately 6 months after the date of randomisation of the first participant. These analyses was carried out to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial. SAE reporting was done in real time according to regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2013
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: 85
Worldwide total number of subjects	85
EEA total number of subjects	85

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)	42
From 65 to 84 years	43

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

85 patients with oesophageal cancer were randomized between October 2013 and February 2015 from 17 UK centers.

Pre-assignment

Screening details:

Eligibility criteria: resectable adenocarcinoma of the oesophagus including Siewert Type 1 or 2 tumor of the gastro-esophageal junction, with cT stage ≥ 3 and/or cN stage ≥ 1 , WHO performance status 0-1, maximum disease (T + N) length 8cm, adequate respiratory, cardiac, hematological, renal and hepatic function, and ≥ 18 years old.

Pre-assignment period milestones

Number of subjects started	205 ^[1]
Number of subjects completed	85

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Declined to participate: 20
Reason: Number of subjects	Other reasons: 2
Reason: Number of subjects	Not meeting inclusion criteria: 98

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 120 participants were excluded following after starting the pre-assignment period

Period 1

Period 1 title	Main 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	OxCapRT

Arm description:

2 cycles OxCap:

Oxaliplatin 130mg/m² Day1

Capecitabine 625mg/m² bd Day 1- 21

then CRT:

Oxaliplatin 85mg/m² Days 1, 15, 29;

Capecitabine 625mg/m² bd only on days when receiving RT

XRT: 45 Gy in 25 fractions

Arm type	Experimental
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

85 mg/m² intravenously on days 1, 15, 29

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

625 mg/m² bd orally on days of radiotherapy

Arm title	CarPacRT
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Arm description:

2 cycles OxCap:

Oxaliplatin 130mg/m² Day 1

Capecitabine 625mg/m² bd Day 1- 21

then CRT:

Paclitaxel 50mg/m² Days 1,8,15,22,29;

Carboplatin AUC 2 Days 1,8,15,22,29

XRT: 45 Gy in 25 fractions

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

Dosage and administration details:

administered intravenously on days 1, 8, 15, 22, 29 of radithery

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

Dosage and administration details:

50 mg/m² administered intravenously on days 1, 8, 15, 22, 29 of radiotherapy

Number of subjects in period 1	OxCapRT	CarPacRT
Started	42	43
Randomisation	42	43
Start OxCap CT	42	43
Start CRT	38	42
Surgery	36	41
Completed	36	41
Not completed	6	2
Adverse event, serious fatal	2	1
Disease progression	3	1
Cirrhotic liver	1	-

Baseline characteristics

Reporting groups

Reporting group title	OxCapRT
Reporting group description:	
2 cycles OxCap:	
Oxaliplatin 130mg/m ² Day1	
Capecitabine 625mg/m ² bd Day 1- 21	
then CRT:	
Oxaliplatin 85mg/m ² Days 1, 15, 29;	
Capecitabine 625mg/m ² bd only on days when receiving RT	
XRT: 45 Gy in 25 fractions	
Reporting group title	CarPacRT
Reporting group description:	
2 cycles OxCap:	
Oxaliplatin 130mg/m ² Day 1	
Capecitabine 625mg/m ² bd Day 1- 21	
then CRT:	
Paclitaxel 50mg/m ² Days 1,8,15,22,29;	
Carboplatin AUC 2 Days 1,8,15,22,29	
XRT: 45 Gy in 25 fractions	

Reporting group values	OxCapRT	CarPacRT	Total
Number of subjects	42	43	85
Age categorical			
Units: Subjects			
Adults (18-64 years)	20	22	42
From 65-84 years	22	21	43
85 years and over	0	0	0
Age continuous			
Units: years			
median	65	64	
full range (min-max)	46 to 77	29 to 76	-
Gender categorical			
Units: Subjects			
Female	7	10	17
Male	35	33	68
cT stage			
Units: Subjects			
T2	6	3	9
T3	36	37	73
T4a	0	3	3
cN stage			
Units: Subjects			
N0	12	16	28
N1	21	20	41
N2	8	6	14
N3	1	1	2
Site of predominant tumour			
Units: Subjects			
Middle third (24 <= 32cm)	6	2	8
Lower third (32 - 40cm)	32	39	71

Missing	4	2	6
WHO performance status			
Units: Subjects			
Zero	37	35	72
One	5	8	13
Maximum total disease length from EUS, PET and CT			
Units: cm			
median	5.85	5.7	
full range (min-max)	2 to 8	2 to 8.3	-
Time from randomisation to start of treatment			
Units: day			
median	4	4	
full range (min-max)	0 to 18	0 to 14	-
Time from staging scan to randomisation			
Units: day			
median	27	28	
full range (min-max)	8 to 56	2 to 51	-

End points

End points reporting groups

Reporting group title	OxCapRT
Reporting group description: 2 cycles OxCap: Oxaliplatin 130mg/m2 Day1 Capecitabine 625mg/m2 bd Day 1- 21 then CRT: Oxaliplatin 85mg/m2 Days 1, 15, 29; Capecitabine 625mg/m2 bd only on days when receiving RT XRT: 45 Gy in 25 fractions	
Reporting group title	CarPacRT
Reporting group description: 2 cycles OxCap: Oxaliplatin 130mg/m2 Day 1 Capecitabine 625mg/m2 bd Day 1- 21 then CRT: Paclitaxel 50mg/m2 Days 1,8,15,22,29; Carboplatin AUC 2 Days 1,8,15,22,29 XRT: 45 Gy in 25 fractions	

Primary: Pathological complete response rate (pCR)

End point title	Pathological complete response rate (pCR) ^[1]
End point description: Pathological complete response rate (pCR) to be assessed in patients undergoing resection following neo-adjuvant treatment, as measured using standardised histological interpretation.	
End point type	Primary
End point timeframe: Review of disease status performed at 30 days, 6 months and 12 months following surgery.	
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: No statistical analyses were used	

End point values	OxCapRT	CarPacRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	41		
Units: Patients	4	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Circumferential resection margin positivity rate

End point title	Circumferential resection margin positivity rate
End point description: A resection margin was defined as being positive when tumour cells were present directly at the resection margin or within 1 mm of the resection margin.	
End point type	Secondary

End point timeframe:

Surgery

End point values	OxCapRT	CarPacRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	41		
Units: Patients				
Tumour at CRM	2	3		
Tumour within 1 mm of CRM	8	5		
No tumour within 1 mm	26	33		

Statistical analyses

No statistical analyses for this end point

Secondary: Peri-operative mortality

End point title Peri-operative mortality

End point description:

End point type Secondary

End point timeframe:

30 day post operative

End point values	OxCapRT	CarPacRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	43		
Units: Patients	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Peri-operative morbidity

End point title Peri-operative morbidity

End point description:

End point type Secondary

End point timeframe:

30 day post operative

End point values	OxCapRT	CarPacRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	43		
Units: Patients				
Any complication	19	21		
Respiratory complication	14	15		
Cardiac complication	9	4		
Wound infection	3	5		
Chylothorax requiring treatment	1	2		
Haemorrhage requiring transfusion or intervention	2	0		
Other complications	9	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During treatment

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.03
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Reporting groups

Reporting group title	Both arms
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Reporting group description:

Both arms received induction chemotherapy

Reporting group title	OxCapRT
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Reporting group description: -

Reporting group title	CarPacRT
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Reporting group description: -

Serious adverse events	Both arms	OxCapRT	CarPacRT
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 85 (31.76%)	16 / 38 (42.11%)	22 / 43 (51.16%)
number of deaths (all causes)	2	3	2
number of deaths resulting from adverse events			
Investigations			
Lymphocyte count decreased	Additional description: Grade III/IV toxicity		
subjects affected / exposed	0 / 85 (0.00%)	3 / 38 (7.89%)	3 / 43 (6.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased	Additional description: Grade III/IV toxicity		
subjects affected / exposed	1 / 85 (1.18%)	1 / 38 (2.63%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased	Additional description: Grade III/IV toxicity		
subjects affected / exposed	0 / 85 (0.00%)	1 / 38 (2.63%)	9 / 43 (20.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased	Additional description: Grade III/IV toxicity		

subjects affected / exposed	0 / 85 (0.00%)	2 / 38 (5.26%)	2 / 43 (4.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall	Additional description: Grade III/IV toxicity		
subjects affected / exposed	0 / 85 (0.00%)	1 / 38 (2.63%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension	Additional description: Grade III/IV toxicity		
subjects affected / exposed	1 / 85 (1.18%)	1 / 38 (2.63%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension	Additional description: Grade III/IV toxicity		
subjects affected / exposed	0 / 85 (0.00%)	0 / 38 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia	Additional description: Grade III/IV toxicity		
subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thromboembolic events	Additional description: Grade III/IV toxicity		
subjects affected / exposed	1 / 85 (1.18%)	1 / 38 (2.63%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Chest pain	Additional description: Grade III/IV toxicity		
subjects affected / exposed	2 / 85 (2.35%)	0 / 38 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Peripheral neuropathy	Additional description: Grade III/IV toxicity		

subjects affected / exposed	5 / 85 (5.88%)	0 / 38 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngolaryngeal dysaesthesia	Additional description: Grade III/IV toxicity		
subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia	Additional description: Grade III/IV toxicity		
subjects affected / exposed	1 / 85 (1.18%)	1 / 38 (2.63%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia	Additional description: Grade III/IV toxicity		
subjects affected / exposed	0 / 85 (0.00%)	0 / 38 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Any haematological toxicity	Additional description: Grade III/IV toxicity		
subjects affected / exposed	2 / 85 (2.35%)	6 / 38 (15.79%)	12 / 43 (27.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue	Additional description: Grade III/IV toxicity		
subjects affected / exposed	9 / 85 (10.59%)	4 / 38 (10.53%)	6 / 43 (13.95%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain	Additional description: Grade III/IV toxicity		
subjects affected / exposed	2 / 85 (2.35%)	1 / 38 (2.63%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic spasm	Additional description: Grade III/IV toxicity		
subjects affected / exposed	0 / 85 (0.00%)	1 / 38 (2.63%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Constipation	Additional description: Grade III/IV toxicity			
	subjects affected / exposed	0 / 85 (0.00%)	1 / 38 (2.63%)	0 / 43 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea	Additional description: Grade III/IV toxicity			
	subjects affected / exposed	7 / 85 (8.24%)	0 / 38 (0.00%)	1 / 43 (2.33%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dry mouth				
	subjects affected / exposed	1 / 85 (1.18%)	1 / 38 (2.63%)	0 / 43 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia				
	subjects affected / exposed	6 / 85 (7.06%)	2 / 38 (5.26%)	2 / 43 (4.65%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage	Additional description: Grade III/IV toxicity			
	subjects affected / exposed	0 / 85 (0.00%)	0 / 38 (0.00%)	1 / 43 (2.33%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucositis	Additional description: Grade III/IV toxicity			
	subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	0 / 43 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea/vomitting	Additional description: Grade III/IV toxicity			
	subjects affected / exposed	6 / 85 (7.06%)	0 / 38 (0.00%)	0 / 43 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal pain	Additional description: Grade III/IV toxicity			
	subjects affected / exposed	0 / 85 (0.00%)	0 / 38 (0.00%)	1 / 43 (2.33%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis	Additional description: Grade III/IV toxicity			

subjects affected / exposed	1 / 85 (1.18%)	2 / 38 (5.26%)	2 / 43 (4.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Grade III/IV toxicity		
subjects affected / exposed	1 / 85 (1.18%)	0 / 38 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Anorexia	Additional description: Grade III/IV toxicity		
subjects affected / exposed	2 / 85 (2.35%)	2 / 38 (5.26%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other	Additional description: Grade III/IV toxicity		
subjects affected / exposed	4 / 85 (4.71%)	0 / 38 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Both arms	OxCapRT	CarPacRT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 85 (89.41%)	35 / 38 (92.11%)	41 / 43 (95.35%)
Vascular disorders			
Hypotension	Additional description: Grade I/II toxicity		
subjects affected / exposed	2 / 85 (2.35%)	0 / 38 (0.00%)	5 / 43 (11.63%)
occurrences (all)	0	0	0
Thromboembolic event	Additional description: Grade I/II toxicity		
subjects affected / exposed	25 / 85 (29.41%)	14 / 38 (36.84%)	22 / 43 (51.16%)
occurrences (all)	0	0	0
Hypertension	Additional description: Grade I/II toxicity		
subjects affected / exposed	23 / 85 (27.06%)	14 / 38 (36.84%)	20 / 43 (46.51%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	Additional description: Grade I/II toxicity		
	59 / 85 (69.41%)	32 / 38 (84.21%)	40 / 43 (93.02%)
	0	0	0
Fever subjects affected / exposed occurrences (all)	Additional description: Grade I/II toxicity		
	4 / 85 (4.71%)	1 / 38 (2.63%)	5 / 43 (11.63%)
	0	0	0
Immune system disorders Allergic reaction subjects affected / exposed occurrences (all)	Additional description: Grade I/II toxicity		
	3 / 85 (3.53%)	1 / 38 (2.63%)	1 / 43 (2.33%)
	0	0	0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all)	Additional description: Grade I/II toxicity		
	6 / 85 (7.06%)	7 / 38 (18.42%)	15 / 43 (34.88%)
	0	0	0
	Additional description: Grade I/II toxicity		
	23 / 85 (27.06%)	14 / 38 (36.84%)	20 / 43 (46.51%)
	0	0	0
Investigations Creatinine increased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all) Lymphocyte count decreased subjects affected / exposed occurrences (all)	Additional description: Grade I/II toxicity		
	6 / 85 (7.06%)	4 / 38 (10.53%)	3 / 43 (6.98%)
	0	0	0
	Additional description: Grade I/II toxicity		
	19 / 85 (22.35%)	22 / 38 (57.89%)	21 / 43 (48.84%)
	0	0	0
	Additional description: Grade I/II toxicity		
	12 / 85 (14.12%)	11 / 38 (28.95%)	22 / 43 (51.16%)
	0	0	0
	Additional description: Grade I/II toxicity		
	26 / 85 (30.59%)	16 / 38 (42.11%)	20 / 43 (46.51%)
	0	0	0
	Additional description: Grade I/II toxicity		
	27 / 85 (31.76%)	17 / 38 (44.74%)	20 / 43 (46.51%)
	0	0	0
Injury, poisoning and procedural complications Fall	Additional description: Grade I/II toxicity		

subjects affected / exposed occurrences (all)	23 / 85 (27.06%) 0	14 / 38 (36.84%) 0	20 / 43 (46.51%) 0
Nervous system disorders			
Sensory neuropathy	Additional description: Grade I/II toxicity		
subjects affected / exposed occurrences (all)	66 / 85 (77.65%) 0	33 / 38 (86.84%) 0	28 / 43 (65.12%) 0
Blood and lymphatic system disorders			
Anaemia	Additional description: Grade I/II toxicity		
subjects affected / exposed occurrences (all)	22 / 85 (25.88%) 0	13 / 38 (34.21%) 0	21 / 43 (48.84%) 0
Febrile neutropenia	Additional description: Grade I/II toxicity		
subjects affected / exposed occurrences (all)	23 / 85 (27.06%) 0	14 / 38 (36.84%) 0	20 / 43 (46.51%) 0
Ear and labyrinth disorders			
Hearing impaired	Additional description: Grade I/II toxicity		
subjects affected / exposed occurrences (all)	3 / 85 (3.53%) 0	0 / 38 (0.00%) 0	0 / 43 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain	Additional description: Grade I/II toxicity		
subjects affected / exposed occurrences (all)	16 / 85 (18.82%) 0	6 / 38 (15.79%) 0	14 / 43 (32.56%) 0
Constipation	Additional description: Grade I/II toxicity		
subjects affected / exposed occurrences (all)	27 / 85 (31.76%) 0	11 / 38 (28.95%) 0	15 / 43 (34.88%) 0
Diarrhoea	Additional description: Grade I/II toxicity		
subjects affected / exposed occurrences (all)	30 / 85 (35.29%) 0	14 / 38 (36.84%) 0	13 / 43 (30.23%) 0
Gastrointestinal haemorrhage	Additional description: Grade I/II toxicity		
subjects affected / exposed occurrences (all)	1 / 85 (1.18%) 0	1 / 38 (2.63%) 0	1 / 43 (2.33%) 0
Mucositis	Additional description: Grade I/II toxicity		
subjects affected / exposed occurrences (all)	12 / 85 (14.12%) 0	5 / 38 (13.16%) 0	9 / 43 (20.93%) 0
Nausea/vomitting	Additional description: Grade I/II toxicity		
subjects affected / exposed occurrences (all)	52 / 85 (61.18%) 52	22 / 38 (57.89%) 22	26 / 43 (60.47%) 26
Oesophagitis	Additional description: Grade I/II toxicity		

subjects affected / exposed	10 / 85 (11.76%)	20 / 38 (52.63%)	23 / 43 (53.49%)
occurrences (all)	0	0	0
Dysaesthesia pharynx	Additional description: Grade I/II toxicity		
subjects affected / exposed	17 / 85 (20.00%)	4 / 38 (10.53%)	3 / 43 (6.98%)
occurrences (all)	0	0	0
Dyspnoea	Additional description: Grade I/II toxicity		
subjects affected / exposed	14 / 85 (16.47%)	10 / 38 (26.32%)	10 / 43 (23.26%)
occurrences (all)	0	0	0
Dysphagia	Additional description: Grade I/II toxicity		
subjects affected / exposed	33 / 85 (38.82%)	16 / 38 (42.11%)	21 / 43 (48.84%)
occurrences (all)	0	0	0
Dry mouth	Additional description: Grade I/II toxicity		
subjects affected / exposed	24 / 85 (28.24%)	14 / 38 (36.84%)	21 / 43 (48.84%)
occurrences (all)	0	0	0
Oesophageal pain	Additional description: Grade I/II toxicity		
subjects affected / exposed	23 / 85 (27.06%)	14 / 38 (36.84%)	20 / 43 (46.51%)
occurrences (all)	0	0	0
Colonic spasm	Additional description: Grade I/II toxicity		
subjects affected / exposed	23 / 85 (27.06%)	14 / 38 (36.84%)	20 / 43 (46.51%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome	Additional description: Grade I/II toxicity		
subjects affected / exposed	9 / 85 (10.59%)	5 / 38 (13.16%)	8 / 43 (18.60%)
occurrences (all)	0	0	0
Rash	Additional description: Grade I/II toxicity		
subjects affected / exposed	8 / 85 (9.41%)	7 / 38 (18.42%)	6 / 43 (13.95%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Chronic kidney disease	Additional description: Grade I/II toxicity		
subjects affected / exposed	3 / 85 (3.53%)	0 / 38 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	0
Infections and infestations			
Infection	Additional description: Grade I/II toxicity		
subjects affected / exposed	6 / 85 (7.06%)	4 / 38 (10.53%)	6 / 43 (13.95%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Anorexia subjects affected / exposed occurrences (all)	Additional description: Grade I/II toxicity		
	27 / 85 (31.76%)	16 / 38 (42.11%)	18 / 43 (41.86%)
	0	0	0
Hypokalaemia subjects affected / exposed occurrences (all)	Additional description: Grade I/II toxicity		
	9 / 85 (10.59%)	4 / 38 (10.53%)	5 / 43 (11.63%)
	0	0	0
Hypomagnesaemia subjects affected / exposed occurrences (all)	Additional description: Grade I/II toxicity		
	7 / 85 (8.24%)	2 / 38 (5.26%)	9 / 43 (20.93%)
	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 November 2013	Protocol updated from version 1.0 to 1.1 - minor amendments to Safety reporting and pharmacovigilance and Appendices
31 January 2014	Protocol version 1.1 superseded by version 2 - Minor Amendment, clarification of eligibility criteria - Major Amendment, removal of undifferentiated oesophageal cancer from trial eligibility and clarification of eligibility criteria - Minor Amendment, additional detail added to trial set up - Minor amendment, inclusion of time restraint between randomisation and treatment start. Clarification that chemoradiotherapy should start immediately post chemotherapy. Minor amendment, inclusion of time restraint between randomisation and treatment start. Clarification that chemoradiotherapy should start immediately post chemotherapy. - Minor amendment to IMP administration due to capecitabine coming off patent. - Major amendment to dose modification for neurotoxicity - Major amendment to dose modification for Diarrhoea, stomatitis, nausea/vomiting toxicities. - Major amendment, additional guidance regarding dose modification for grade 2 Diarrhoea, stomatitis, nausea/ vomiting - Major amendment, additional guidance regarding oxaliplatin dose modification for neurotoxicity during chemo-radiotherapy. - Minor amendment, Insertion (additional guidance for patients discontinuing treatment due to Non-haematological toxicity) - Major amendment, Additional instruction regarding carboplatin dose capping - Minor amendment, Increased flexibility to surgical procedure - Minor amendment, inclusion of flexibility to timing of trial assessments
19 May 2015	Protocol v2 superseded by v3 - Minor Amendment, RSI dates added to table - Major Amendment, insertion of expected events for surgery - Major Amendment, insertion of expected events for radiotherapy - Major amendment, clarification of translational sample management - Minor amendment, removal of reference to individual trial agreements - Minor amendment, update wording in line with amendment to Welsh Risk Pool Technical Note 12.
28 June 2017	Protocol updated from v3 to v4 - Substantial Amendment, sentence added to trial schema and trial synopsis regarding the extension to follow-up period - Substantial Amendment, changes to section title (Follow up assessment) - extension of follow up period - Substantial Amendment, sentence added changing the end of trial definition due to the extension to the follow up period.

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/28335886>