# 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 |

**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 |

## 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 |
|---|---|

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 raditherapy

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

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

| | | | |
|---|---|---|---|
| Missing | 4 | 2 | 6 |
| WHO performance status<br>Units: Subjects | | | |
| Zero | 37 | 35 | 72 |
| One | 5 | 8 | 13 |
| Maximum total disease length from EUS, PET and CT<br>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<br>Units: day | | | |
| median | 4 | 4 | |
| full range (min-max) | 0 to 18 | 0 to 14 | - |
| Time from staging scan to randomisation<br>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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | CTCAE |
| Dictionary version | 4.03 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Both arms |

Reporting group description:

Both arms received induction chemotherapy

| | |
|---|---|
| Reporting group title | OxCapRT |

Reporting group description: -

| | |
|---|---|
| Reporting group title | CarPacRT |

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 | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 59 / 85 (69.41%) | 32 / 38 (84.21%) | 40 / 43 (93.02%) |
| occurrences (all) | 0 | 0 | 0 |
| Fever | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 4 / 85 (4.71%) | 1 / 38 (2.63%) | 5 / 43 (11.63%) |
| occurrences (all) | 0 | 0 | 0 |
| Immune system disorders | | | |
| Allergic reaction | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 3 / 85 (3.53%) | 1 / 38 (2.63%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 6 / 85 (7.06%) | 7 / 38 (18.42%) | 15 / 43 (34.88%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest 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 |
| Investigations | | | |
| Creatinine increased | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 6 / 85 (7.06%) | 4 / 38 (10.53%) | 3 / 43 (6.98%) |
| occurrences (all) | 0 | 0 | 0 |
| Platelet count decreased | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 19 / 85 (22.35%) | 22 / 38 (57.89%) | 21 / 43 (48.84%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutrophil count decreased | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 12 / 85 (14.12%) | 11 / 38 (28.95%) | 22 / 43 (51.16%) |
| occurrences (all) | 0 | 0 | 0 |
| White blood cell count decreased | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 26 / 85 (30.59%) | 16 / 38 (42.11%) | 20 / 43 (46.51%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphocyte count decreased | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 27 / 85 (31.76%) | 17 / 38 (44.74%) | 20 / 43 (46.51%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | 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 |
| Nervous system disorders | | | |
| Sensory neuropathy | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 66 / 85 (77.65%) | 33 / 38 (86.84%) | 28 / 43 (65.12%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 22 / 85 (25.88%) | 13 / 38 (34.21%) | 21 / 43 (48.84%) |
| occurrences (all) | 0 | 0 | 0 |
| Febrile neutropenia | 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 |
| Ear and labyrinth disorders | | | |
| Hearing impaired | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 3 / 85 (3.53%) | 0 / 38 (0.00%) | 0 / 43 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 16 / 85 (18.82%) | 6 / 38 (15.79%) | 14 / 43 (32.56%) |
| occurrences (all) | 0 | 0 | 0 |
| Constipation | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 27 / 85 (31.76%) | 11 / 38 (28.95%) | 15 / 43 (34.88%) |
| occurrences (all) | 0 | 0 | 0 |
| Diarrhoea | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 30 / 85 (35.29%) | 14 / 38 (36.84%) | 13 / 43 (30.23%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal haemorrhage | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 1 / 38 (2.63%) | 1 / 43 (2.33%) |
| occurrences (all) | 0 | 0 | 0 |
| Mucositis | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 12 / 85 (14.12%) | 5 / 38 (13.16%) | 9 / 43 (20.93%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea/vomitting | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 52 / 85 (61.18%) | 22 / 38 (57.89%) | 26 / 43 (60.47%) |
| occurrences (all) | 52 | 22 | 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 | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 27 / 85 (31.76%) | 16 / 38 (42.11%) | 18 / 43 (41.86%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypokalaemia | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 9 / 85 (10.59%) | 4 / 38 (10.53%) | 5 / 43 (11.63%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypomagnesaemia | Additional description: Grade I/II toxicity | | |
| subjects affected / exposed | 7 / 85 (8.24%) | 2 / 38 (5.26%) | 9 / 43 (20.93%) |
| occurrences (all) | 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<br>- Minor Amendment, clarification of eligibility criteria<br>- Major Amendment, removal of undifferentiated oesophageal cancer from trial eligibility and clarification of eligibility criteria<br>- Minor Amendment, additional detail added to trial set up<br>- 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.<br>- Minor amendment to IMP administration due to capecitabine coming off patent.<br>- Major amendment to dose modification for neurotoxicity<br>- Major amendment to dose modification for Diarrhoea, stomatitis, nausea/vomiting toxicities.<br>- Major amendment, additional guidance regarding dose modification for grade 2 Diarrhoea, stomatitis, nausea/ vomiting<br>- Major amendment, additional guidance regarding oxaliplatin dose modification for neurotoxicity during chemo-radiotherapy.<br>- Minor amendment, Insertion (additional guidance for patients discontinuing treatment due to Non-haematological toxicity)<br>- Major amendment, Additional instruction regarding carboplatin dose capping<br>- Minor amendment, Increased flexibility to surgical procedure<br>- Minor amendment, inclusion of flexibility to timing of trial assessments |
| 19 May 2015 | Protocol v2 superseded by v3<br>- Minor Amendment, RSI dates added to table<br>- Major Amendment, insertion of expected events for surgery<br>- Major Amendment, insertion of expected events for radiotherapy<br>- Major amendment, clarification of translational sample management<br>- Minor amendment, removal of reference to individual trial agreements<br>- Minor amendment, update wording in line with amendment to Welsh Risk Pool Technical Note 12. |
| 28 June 2017 | Protocol updated from v3 to v4<br>- Substantial Amendment, sentence added to trial schema and trial synopsis regarding the extension to follow-up period<br>- Substantial Amendment, changes to section title (Follow up assessment) - extension of follow up period<br>- 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