Clinical trial results:
Neo-AEGIS (NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric Junction International Study): Randomised Clinical Trial of neoadjuvant and adjuvant chemotherapy (Investigator's choice Modified MAGIC or FLOT regimen) vs. neoadjuvant chemoradiation (CROSS protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction

Summary

EudraCT number	2011-001858-28
Trial protocol	IE DK GB FR SE
Global end of trial date	04 August 2022

Results information

Result version number	v1 (current)
This version publication date	16 December 2023
First version publication date	16 December 2023

Trial information

Trial identification

Sponsor protocol code	CTRIAL-IE (ICORG) 10-14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01726452
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cancer Trials Ireland
Sponsor organisation address	RCSI House, Dublin, Ireland, D02 H903
Public contact	Head of Clinical Operations, Cancer Trials Ireland, 00353 16677211, info@cancertrials.ie
Scientific contact	Head of Clinical Operations, Cancer Trials Ireland, 00353 16677211, info@cancertrials.ie

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	19 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 August 2022
Global end of trial reached?	Yes
Global end of trial date	04 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate one, two and three year survival of patients treated with resection plus neoadjuvant and adjuvant chemotherapy versus resection plus neoadjuvant chemo radiotherapy.

Protection of trial subjects:

This clinical study was conducted in accordance with the EU Directive 2001/20/EC and International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP) and the appropriate regulatory requirements. The trial was also conducted in accordance with ethical principles founded in the Declaration of Helsinki.

Background therapy:

N/A

Evidence for comparator:

The primary objective is to compare neoadjuvant and adjuvant chemotherapy (ARM A: Investigator's choice modified MAGIC or FLOT regimen) versus neoadjuvant chemoradiation (ARM B: CROSS Protocol) in adenocarcinoma of the oesophagus and oesophago-gastric junction.

Actual start date of recruitment	24 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	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 199
Country: Number of subjects enrolled	Denmark: 38
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Ireland: 134
Worldwide total number of subjects	377
EEA total number of subjects	178

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)	194
From 65 to 84 years	183
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

377 patients were recruited across 24 sites between 24-Jan-2013 and 23-Dec-2020

Pre-assignment

Screening details:

Patients presenting with newly diagnosed cancer of the oesophagus or oesophago-gastric junction, pre-treatment stage cT2-3, N0-3, M0 who fulfill all of the inclusion criteria and none of the exclusion criteria.

Period 1

Period 1 title	Overall Trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: neoadjuvant and adjuvant chemotherapy

Arm description:

Arm A consists of chemotherapy pre-surgery and chemotherapy post-surgery. The chemotherapy regimens included in Neo-Aegis are included as accepted standards of care. Decisions about which chemotherapy regimen to use, i.e. modified MAGIC (ECF/ECX or EOF/EOX) or FLOT, are to be made by the treating clinician.

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

Dosage and administration details:

MAGIC Regimen: 50 mg/m2

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	PA0822-199-001
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Concentrate for solution for infusion , Infusion

Dosage and administration details:

MAGIC Regimen: 60 mg/m2

Investigational medicinal product name	5-fluorouracil
Investigational medicinal product code	PA2315-091-001
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

MAGIC regimen: 200 mg/m2/Day
FLOT: 2600 mg/m2

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

Dosage and administration details: FLOT Regimen: 50 mg/m²	
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	Eloxatin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Magic Regimen: 130 mg/m² FLOT Regimen: 85 mg/m²	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: FLOT Regimen: 200 mg/m²	
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: MAGIC Regimen: 625 mg/m2 twice daily	

Arm title	Arm B - neoadjuvant chemoradiation

Arm description:

Arm B consists of the multimodal CROSS arm, which includes a combination of chemotherapy and radiotherapy prior to surgery. The patient will receive four and a half (4.5) weeks of radiation therapy (41.4 Gy/23 fractions), and 5 weekly cycles of chemotherapy. The chemotherapy and radiotherapy will run concurrently over a 4 and a half-week period. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29. The radiation will generally commence on the 1st day of treatment and will run for 4 and a half weeks as follows: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive.

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	PA2315-091-001
Other name	
Pharmaceutical forms	Concentrate for dispersion for infusion
Routes of administration	Infusion
Dosage and administration details: 50 mg/ m2	
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion
Dosage and administration details: The absolute dose of carboplatin will be calculated for the target Area Under the Curve (AUC)=2 according to the Calvert formula with a maximum weekly dose of Carboplatin of 300mg.	

Number of subjects in period 1	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B - neoadjuvant chemoradiation
Started	189	188
Completed	184	178
Not completed	5	10
Ineligible	2	3
Patient decision	3	4
Adverse event	-	1
Investigator decision	-	2

Period 2

Period 2 title	Intention to treat IITT)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: neoadjuvant and adjuvant chemotherapy

Arm description:

Arm A consists of chemotherapy pre-surgery and chemotherapy post-surgery. The chemotherapy regimens included in Neo-Aegis are included as accepted standards of care. Decisions about which chemotherapy regimen to use, i.e. modified MAGIC (ECF/ECX or EOF/EOX) or FLOT, are to be made by the treating clinician.

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

Dosage and administration details:

MAGIC Regimen: 50 mg/m2

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	PA0822-199-001
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion , Infusion

Dosage and administration details:

MAGIC Regimen: 60 mg/m2

Investigational medicinal product name	5-fluorouracil
Investigational medicinal product code	PA2315-091-001
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

MAGIC regimen: 200 mg/m2/Day

FLOT: 2600 mg/m2

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

Dosage and administration details:

FLOT Regimen: 50 mg/m²

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

Dosage and administration details:

Magic Regimen: 130 mg/m²
FLOT Regimen: 85 mg/m²

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

Dosage and administration details:

FLOT Regimen: 200 mg/m²

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

MAGIC Regimen: 625 mg/m2 twice daily

Arm title	Arm B: neoadjuvant chemoradiation

Arm description:

Arm B consists of the multimodal CROSS arm, which includes a combination of chemotherapy and radiotherapy prior to surgery. The patient will receive four and a half (4.5) weeks of radiation therapy (41.4 Gy/23 fractions), and 5 weekly cycles of chemotherapy. The chemotherapy and radiotherapy will run concurrently over a 4 and a half-week period. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29. The radiation will generally commence on the 1st day of treatment and will run for 4 and a half weeks as follows: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive.

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	PA2315-091-001
Other name	
Pharmaceutical forms	Concentrate for dispersion for infusion
Routes of administration	Infusion

Dosage and administration details:

50 mg/ m2

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

The absolute dose of carboplatin will be calculated for the target Area Under the Curve (AUC)=2 according to the Calvert formula with a maximum weekly dose of Carboplatin of 300mg.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The primary and secondary analysis were performed on an intention to treat (ITT) basis. There were 362 participants in this set.

Number of subjects in period 2[2]	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation
Started	184	178
Completed	183	178
Not completed	1	0
Adverse event, non-fatal	1	-

Notes:

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

Justification: The primary and secondary analysis were performed on an intention to treat (ITT) basis. There were 362 participants in this set.

Period 3

Period 3 title	Safety Set
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: neoadjuvant and adjuvant chemotherapy

Arm description:

Arm A consists of chemotherapy pre-surgery and chemotherapy post-surgery. The chemotherapy regimens included in Neo-Aegis are included as accepted standards of care. Decisions about which chemotherapy regimen to use, i.e. modified MAGIC (ECF/ECX or EOF/EOX) or FLOT, are to be made by the treating clinician.

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

Dosage and administration details:

MAGIC Regimen: 50 mg/m2

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	PA0822-199-001
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

MAGIC Regimen: 60 mg/m2

Investigational medicinal product name	5-fluorouracil
Investigational medicinal product code	PA2315-091-001
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

MAGIC regimen: 200 mg/m2/Day
FLOT: 2600 mg/m2

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

Dosage and administration details:

FLOT Regimen: 50 mg/m²

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

Dosage and administration details:

Magic Regimen: 130 mg/m²
FLOT Regimen: 85 mg/m²

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

Dosage and administration details:

FLOT Regimen: 200 mg/m²

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

MAGIC Regimen: 625 mg/m2 twice daily

Arm title	Arm B: neoadjuvant chemoradiation

Arm description:

Arm B consists of the multimodal CROSS arm, which includes a combination of chemotherapy and radiotherapy prior to surgery. The patient will receive four and a half (4.5) weeks of radiation therapy (41.4 Gy/23 fractions), and 5 weekly cycles of chemotherapy. The chemotherapy and radiotherapy will run concurrently over a 4 and a half-week period. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29. The radiation will generally commence on the 1st day of treatment and will run for 4 and a half weeks as follows: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive.

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	PA2315-091-001
Other name	
Pharmaceutical forms	Concentrate for dispersion for infusion
Routes of administration	Infusion

Dosage and administration details: 50 mg/ m2	
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

The absolute dose of carboplatin will be calculated for the target Area Under the Curve (AUC)=2 according to the Calvert formula with a maximum weekly dose of Carboplatin of 300mg.

Number of subjects in period 3	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation
Started	183	178
Completed	183	178

Baseline characteristics

Reporting groups

Reporting group title	Arm A: neoadjuvant and adjuvant chemotherapy

Reporting group description:

Arm A consists of chemotherapy pre-surgery and chemotherapy post-surgery. The chemotherapy regimens included in Neo-Aegis are included as accepted standards of care. Decisions about which chemotherapy regimen to use, i.e. modified MAGIC (ECF/ECX or EOF/EOX) or FLOT, are to be made by the treating clinician.

Reporting group title	Arm B: neoadjuvant chemoradiation

Reporting group description:

Arm B consists of the multimodal CROSS arm, which includes a combination of chemotherapy and radiotherapy prior to surgery. The patient will receive four and a half (4.5) weeks of radiation therapy (41.4 Gy/23 fractions), and 5 weekly cycles of chemotherapy. The chemotherapy and radiotherapy will run concurrently over a 4 and a half-week period. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29. The radiation will generally commence on the 1st day of treatment and will run for 4 and a half weeks as follows: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive.

Reporting group values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation	Total
Number of subjects	184	178	362
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)	93	92	185
From 65-84 years	91	86	177
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	63.8	63.8	
standard deviation	± 8.8	± 7.9	-
Gender categorical Units: Subjects			
Female	15	20	35
Male	169	158	327
Ethnic Origin Units: Subjects			
Caucasian	183	177	360
Asian	1	1	2
Smoking status at baseline Units: Subjects			
Never	58	52	110
Past Smoker	101	106	207
Current Smoker	23	20	43

Missing value	2	0	2
ECOG at baseline Units: Subjects			
Grade 0	155	148	303
Grade 1	27	28	55
Grade 2	2	2	4
American Society of Anaesthesiologists (ASA) at baseline Units: Subjects			
ASA I	86	92	178
ASA II	94	85	179
Missing value	4	1	5
Tumour location Units: Subjects			
Lower Oesophagus or AEG Type I	123	126	249
AEG Type II	46	38	84
AEG Type III	15	14	29
Tumour stage (Primary tumour) Units: Subjects			
T2	29	28	57
T3	155	150	305
Tumour stage (Regional Lymph Nodes) Units: Subjects			
N0	73	78	151
N1	83	73	156
N2	23	27	50
N3	5	0	5
Tumour stage (Distant Metastases) Units: Subjects			
M0	184	178	362
Overall Staging Units: Subjects			
Stage 0	1	0	1
Stage IB	8	10	18
Stage IIA	26	32	58
Stage IIB	55	40	95
Stage IIIA	66	74	140
Stage IIIB	20	21	41
Stage IIIC	4	1	5
Stage IV	1	0	1
Missing value	3	0	3
Node positivity at baseline Units: Subjects			
Positive	57	53	110
Negative	112	109	221
Missing value	15	16	31
BMI at baseline Units: Number			
median	27.2	26.7	
full range (min-max)	18 to 41	18 to 43	-

Subject analysis sets

Subject analysis set title	Intention to treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients randomised into the trial, regardless of what study drug they received, as long as they recieved at least one dose of study drug.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Includes All patients who have taken at least one dose of study drug. There is one less patient in this set compared to the ITT set due to one patient proceeding straight to surgery following an SAE that led to hospitilization after signing of informed consent.

Subject analysis set title	Pre Surgery
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Treatment group after neoadjuvant treatment

Subject analysis set title	1 year Post Surgery
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Treatment group 1 year post surgery

Subject analysis set title	3 Year Post Surgery
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Treatment group 3 years past surgery

Reporting group values	Intention to treat (ITT)	Safety Analysis Set	Pre Surgery
Number of subjects	362	361	332
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	185		
From 65-84 years	177		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	63.8	63.8	
standard deviation	± 8.4	± 8.4	±
Gender categorical Units: Subjects			
Female	35	35	
Male	327	326	
Ethnic Origin Units: Subjects			
Caucasian	360	359	
Asian	2	2	

Smoking status at baseline Units: Subjects			
Never	110	109	
Past Smoker	207	207	
Current Smoker	43	43	
Missing value	2	2	
ECOG at baseline Units: Subjects			
Grade 0	303	302	
Grade 1	55	55	
Grade 2	4	4	
American Society of Anaesthesiologists (ASA) at baseline Units: Subjects			
ASA I	178	177	
ASA II	179	179	
Missing value	5	5	
Tumour location Units: Subjects			
Lower Oesophagus or AEG Type I	249	248	
AEG Type II	84	84	
AEG Type III	29	29	
Tumour stage (Primary tumour) Units: Subjects			
T2	57	57	
T3	305	304	
Tumour stage (Regional Lymph Nodes) Units: Subjects			
N0	151	151	
N1	156	155	
N2	50	50	
N3	5	5	
Tumour stage (Distant Metastases) Units: Subjects			
M0	362	361	
Overall Staging Units: Subjects			
Stage 0	1	1	
Stage IB	18	18	
Stage IIA	58	58	
Stage IIB	95	95	
Stage IIIA	140	139	
Stage IIIB	41	41	
Stage IIIC	5	5	
Stage IV	1	1	
Missing value	3	3	
Node positivity at baseline Units: Subjects			
Positive	110	109	
Negative	221	221	
Missing value	31	31	

BMI at baseline Units: Number			
median	27.0	27.0	
full range (min-max)	18 to 43	18 to 43	

Reporting group values	1 year Post Surgery	3 Year Post Surgery	
Number of subjects	191	89	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	
Gender categorical Units: Subjects			
Female Male			
Ethnic Origin Units: Subjects			
Caucasian Asian			
Smoking status at baseline Units: Subjects			
Never Past Smoker Current Smoker Missing value			
ECOG at baseline Units: Subjects			
Grade 0 Grade 1 Grade 2			
American Society of Anaesthesiologists (ASA) at baseline Units: Subjects			
ASA I ASA II Missing value			
Tumour location Units: Subjects			
Lower Oesophagus or AEG Type I			

AEG Type II			
AEG Type III			
Tumour stage (Primary tumour) Units: Subjects			
T2			
T3			
Tumour stage (Regional Lymph Nodes) Units: Subjects			
N0			
N1			
N2			
N3			
Tumour stage (Distant Metastases) Units: Subjects			
M0			
Overall Staging Units: Subjects			
Stage 0			
Stage IB			
Stage IIA			
Stage IIB			
Stage IIIA			
Stage IIIB			
Stage IIIC			
Stage IV			
Missing value			
Node positivity at baseline Units: Subjects			
Positive			
Negative			
Missing value			
BMI at baseline Units: Number median full range (min-max)			

End points reporting groups

Reporting group title	Arm A: neoadjuvant and adjuvant chemotherapy

Reporting group description:

Arm A consists of chemotherapy pre-surgery and chemotherapy post-surgery. The chemotherapy regimens included in Neo-Aegis are included as accepted standards of care. Decisions about which chemotherapy regimen to use, i.e. modified MAGIC (ECF/ECX or EOF/EOX) or FLOT, are to be made by the treating clinician.

Reporting group title	Arm B - neoadjuvant chemoradiation

Reporting group description:

Arm B consists of the multimodal CROSS arm, which includes a combination of chemotherapy and radiotherapy prior to surgery. The patient will receive four and a half (4.5) weeks of radiation therapy (41.4 Gy/23 fractions), and 5 weekly cycles of chemotherapy. The chemotherapy and radiotherapy will run concurrently over a 4 and a half-week period. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29. The radiation will generally commence on the 1st day of treatment and will run for 4 and a half weeks as follows: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive.

Reporting group title	Arm A: neoadjuvant and adjuvant chemotherapy

Reporting group description:

Arm A consists of chemotherapy pre-surgery and chemotherapy post-surgery. The chemotherapy regimens included in Neo-Aegis are included as accepted standards of care. Decisions about which chemotherapy regimen to use, i.e. modified MAGIC (ECF/ECX or EOF/EOX) or FLOT, are to be made by the treating clinician.

Reporting group title	Arm B: neoadjuvant chemoradiation

Reporting group description:

Arm B consists of the multimodal CROSS arm, which includes a combination of chemotherapy and radiotherapy prior to surgery. The patient will receive four and a half (4.5) weeks of radiation therapy (41.4 Gy/23 fractions), and 5 weekly cycles of chemotherapy. The chemotherapy and radiotherapy will run concurrently over a 4 and a half-week period. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29. The radiation will generally commence on the 1st day of treatment and will run for 4 and a half weeks as follows: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive.

Reporting group title	Arm A: neoadjuvant and adjuvant chemotherapy

Reporting group description:

Arm A consists of chemotherapy pre-surgery and chemotherapy post-surgery. The chemotherapy regimens included in Neo-Aegis are included as accepted standards of care. Decisions about which chemotherapy regimen to use, i.e. modified MAGIC (ECF/ECX or EOF/EOX) or FLOT, are to be made by the treating clinician.

Reporting group title	Arm B: neoadjuvant chemoradiation

Reporting group description:

Arm B consists of the multimodal CROSS arm, which includes a combination of chemotherapy and radiotherapy prior to surgery. The patient will receive four and a half (4.5) weeks of radiation therapy (41.4 Gy/23 fractions), and 5 weekly cycles of chemotherapy. The chemotherapy and radiotherapy will run concurrently over a 4 and a half-week period. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29. The radiation will generally commence on the 1st day of treatment and will run for 4 and a half weeks as follows: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive.

Subject analysis set title	Intention to treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients randomised into the trial, regardless of what study drug they received, as long as they recieved at least one dose of study drug.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Includes All patients who have taken at least one dose of study drug. There is one less patient in this set compared to the ITT set due to one patient proceeding straight to surgery following an SAE that led to hospitilization after signing of informed consent.

Subject analysis set title	Pre Surgery
Subject analysis set type	Sub-group analysis
Subject analysis set description: Treatment group after neoadjuvant treatment	
Subject analysis set title	1 year Post Surgery
Subject analysis set type	Sub-group analysis
Subject analysis set description: Treatment group 1 year post surgery	
Subject analysis set title	3 Year Post Surgery
Subject analysis set type	Sub-group analysis
Subject analysis set description: Treatment group 3 years past surgery	

Primary: Overall Survival

End point title	Overall Survival
End point description:	
End point type	Primary
End point timeframe: Overall survival was calculated from the time of randomisation to death from any cause.	

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	178		
Units: Months				
median (confidence interval 95%)	48.5 (33.1 to 65)	49.6 (34.6 to 74.3)		

Statistical analyses

Statistical analysis title	Hazard Ratio (Overall Survival)
Comparison groups	Arm A: neoadjuvant and adjuvant chemotherapy v Arm B: neoadjuvant chemoradiation
Number of subjects included in analysis	362
Analysis specification	Post-hoc
Analysis type	non-inferiority[1]
P-value	= 0.824
Method	Kaplan-Meier
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.38

Notes:

[1] - The non-inferiority limit of 1.16 is included in the interval and therefore results are inconclusive with no statistical evidence to declare neoadjuvant and adjuvant chemotherapy arm (Arm A) non-inferior to the neoadjuvant chemoradiation arm (Arm B)

Statistical analysis title	Adjusted hazard ration (Age)

Statistical analysis description:

A subgroup analysis was also performed to explore differences in the treatment effect for subsets of participants defined by demographics and baseline characteristics.

Comparison groups	Arm A: neoadjuvant and adjuvant chemotherapy v Arm B: neoadjuvant chemoradiation
Number of subjects included in analysis	362
Analysis specification	Post-hoc
Analysis type	non-inferiority[2]
P-value	= 0.068
Method	Multivariate Cox ph model
Parameter estimate	Cox proportional hazard
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.04

Notes:

[2] - Age

Statistical analysis title	Adjusted hazard ration (Gender: Female vs Male)

Statistical analysis description:

Gender: Female vs Male - A subgroup analysis was also performed to explore differences in the treatment effect for subsets of participants defined by demographics and baseline characteristics.

Comparison groups	Arm A: neoadjuvant and adjuvant chemotherapy v Arm B: neoadjuvant chemoradiation
Number of subjects included in analysis	362
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.481
Method	Multivariate Cox ph model
Parameter estimate	Cox proportional hazard
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.39

Statistical analysis title	Adjusted hazard ration (Primary tumour: T3 vs T2)
Comparison groups	Arm A: neoadjuvant and adjuvant chemotherapy v Arm B: neoadjuvant chemoradiation

Number of subjects included in analysis	362
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.022
Method	Multivariate Cox ph model
Parameter estimate	Cox proportional hazard
Point estimate	1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	2.62

Secondary: Disease Free Survival

End point title	Disease Free Survival

End point description:

End point type	Secondary

End point timeframe:

Disease free survival was calculated from randomisation to the first event (i.e local recurrence or progression, distant recurrence, or death from any cause)

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	178		
Units: Months				
median (confidence interval 95%)	32.1 (22.9 to 65.0)	24.2 (17.5 to 40.3)		

Statistical analyses

Statistical analysis title	Hazard Ratio (Disease free Survival)
Comparison groups	Arm A: neoadjuvant and adjuvant chemotherapy v Arm B: neoadjuvant chemoradiation
Number of subjects included in analysis	362
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.405
Method	Kaplan-Meier
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.17

Statistical analysis title	Adjusted hazard ratio (Age)
Comparison groups	Arm A: neoadjuvant and adjuvant chemotherapy v Arm B: neoadjuvant chemoradiation
Number of subjects included in analysis	362
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.256
Method	Multivariate Cox ph model
Parameter estimate	Cox proportional hazard
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.03

Statistical analysis title	Adjusted hazard ratio (Gender: Female vs Male)
Comparison groups	Arm A: neoadjuvant and adjuvant chemotherapy v Arm B: neoadjuvant chemoradiation
Number of subjects included in analysis	362
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.346
Method	Multivariate Cox ph model
Parameter estimate	Cox proportional hazard
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.29

Statistical analysis title	Adjusted hazard ratio (Primary tumour: T3 vs T2)
Comparison groups	Arm A: neoadjuvant and adjuvant chemotherapy v Arm B: neoadjuvant chemoradiation

Number of subjects included in analysis	362
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.009
Method	Multivariate Cox ph model
Parameter estimate	Cox proportional hazard
Point estimate	1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	2.69

Secondary: Quality of Life - QLQ-C30 Global Health status

End point title	Quality of Life - QLQ-C30 Global Health status

End point description:

The functional derived scores were calculated using the standard EORTC recommended methods. Differences from baseline were compared between arms of the study using independent sample t-tests.

End point type	Secondary

End point timeframe:

The functional and symptomatic scales of the HRQOL questionnaires were examined by calculating the differences in measurements from baseline at specific timepoints.

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	171		
Units: Number				
arithmetic mean (confidence interval 95%)				
Global health Status/QoL	78 (75 to 81)	80 (77 to 82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life - QLQ-C30 Functional Scales

End point title	Quality of Life - QLQ-C30 Functional Scales

End point description:

The functional derived scores were calculated using the standard EORTC recommended methods.

End point type	Secondary

End point timeframe:

The functional scales of the HRQOL questionnaires were examined by calculating the differences in measurements from baseline at specific time points.

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	171		
Units: Number				
arithmetic mean (confidence interval 95%)				
Physical functioning	95 (94 to 97)	95 (94 to 97)		
Role functioning	89 (86 to 92)	92 (89 to 94)		
Emotional functioning	82 (80 to 85)	82 (79 to 85)		
Cognitive functioning	93 (91 to 95)	93 (91 to 95)		
Social functioning	86 (83 to 90)	88 (85 to 91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life - QLQ-C30 Symptom Scales

End point title	Quality of Life - QLQ-C30 Symptom Scales

End point description:

The symptomatic derived scores were calculated using the standard EORTC recommended method.

End point type	Secondary

End point timeframe:

The symptomatic scales of the HRQOL questionnaires were examined by calculating the differences in measurements from baseline at specific time points.

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	171		
Units: Number				
arithmetic mean (confidence interval 95%)				
Fatigue	15 (12 to 17)	15 (13 to 18)		
Nausea and vomiting	9 (6 to 11)	8 (5 to 10)		
Pain	15 (12 to 17)	12 (9 to 14)		
Dyspnoea	3 (2 to 5)	5 (3 to 7)		
Insomnia	21 (17 to 24)	22 (18 to 26)		
Appetite loss	22 (18 to 27)	18 (14 to 22)		
Constipation	15 (11 to 19)	14 (10 to 17)		
Diarrhoea	5 (3 to 7)	6 (3 to 8)		

Financial difficulties	14 (10 to 19)	9 (6 to 13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life - OES-18 Symptom Scales

End point title	Quality of Life - OES-18 Symptom Scales

End point description:

The symptomatic derived scores were calculated using the standard EORTC recommended method.

End point type	Secondary

End point timeframe:

The symptomatic scales of the HRQOL questionnaires were examined by calculating the differences in measurements from baseline at specific time points.

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	171		
Units: Number				
arithmetic mean (confidence interval 95%)				
Eating	32 (28 to 36)	26 (23 to 30)		
Reflux	15 (12 to 18)	12 (9 to 15)		
Pain	17 (14 to 20)	17 (14 to 21)		
Trouble swallowing saliva	12 (8 to 16)	11 (7 to 15)		
Dry mouth	20 (16 to 24)	18 (13 to 22)		
Trouble with taste	8 (5 to 11)	7 (4 to 10)		
Trouble with coughing	8 (5 to 11)	9 (6 to 11)		
Trouble talking	2 (0 to 3)	2 (1 to 4)		
Choked when swallowing	10 (7 to 13)	10 (7 to 13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life - OES-18 Functional Scales

End point title	Quality of Life - OES-18 Functional Scales

End point description:

The functional derived scores were calculated using the standard EORTC recommended methods.

End point type	Secondary

End point timeframe:

The functional scales of the HRQOL questionnaires were examined by calculating the differences in measurements from baseline at specific time points.

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	171		
Units: Number				
arithmetic mean (confidence interval 95%)				
Dysphagia	79 (76 to 82)	77 (73 to 81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Differences in Quality of Life scores - QLQ-C30 Global Health status

End point title	Mean Differences in Quality of Life scores - QLQ-C30 Global Health status

End point description:

The mean difference (MD) from Baseline to different timepoints are adjusted by Baseline scores in a linear model. Differences are calculated as Arm B - Arm A.

End point type	Secondary

End point timeframe:

From baseline to different time points (Pre-surgery, 1 year post surgery and 3 years post surgery)

End point values	Pre Surgery	1 year Post Surgery	3 Year Post Surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	332	191	89	
Units: Mean Difference				
number (confidence interval 95%)				
Global Health Status/QoL	-8 (-12 to -3)	-2 (-8 to 4)	-1 (-9 to 7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Differences in Quality of Life scores - QLQ-C30 Functional Scales

End point title	Mean Differences in Quality of Life scores - QLQ-C30 Functional

	Scales

End point description:

The mean difference (MD) from Baseline to different timepoints are adjusted by Baseline scores in a linear model. Differences are calculated as Arm B - Arm A.

End point type	Secondary

End point timeframe:

From baseline to different time points (Pre-surgery, 1 year post surgery and 3 years post surgery)

End point values	Pre Surgery	1 year Post Surgery	3 Year Post Surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	332	191	89	
Units: Mean Difference				
number (confidence interval 95%)				
Physical functioning	-5 (-8 to -2)	-3 (-8 to 2)	2 (-6 to 11)	
Role functioning	-6 (-12 to 1)	-3 (-11 to 6)	-4 (-15 to 7)	
Emotional functioning	-5 (-9 to -1)	-7 (-13 to -1)	-1 (-10 to 9)	
Cognitive functioning	-1 (-5 to 3)	2 (-4 to 8)	0 (-9 to 9)	
Social functioning	-4 (-9 to 2)	0 (-8 to 8)	2 (-9 to 13)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Differences in Quality of Life scores- QLQ-C30 Symptom Scales

End point title	Mean Differences in Quality of Life scores- QLQ-C30 Symptom Scales

End point description:

The mean difference (MD) from Baseline to different timepoints are adjusted by Baseline scores in a linear model. Differences are calculated as Arm B - Arm A.

End point type	Secondary

End point timeframe:

From baseline to different time points (Pre-surgery, 1 year post surgery and 3 years post surgery)

End point values	Pre Surgery	1 year Post Surgery	3 Year Post Surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	332	191	89	
Units: Mean Difference				
number (confidence interval 95%)				
Fatique	8 (3 to 13)	-1 (-8 to 6)	-2 (-13 to 9)	
Nausea and vomiting	2 (-2 to 5)	2 (-3 to 7)	-2 (-10 to 6)	
Pain	8 (3 to 12)	8 (0 to 16)	1 (-10 to 11)	
Dyspnoea	2 (-2 to 7)	6 (-2 to 13)	-1 (-13 to 11)	
Insomnia	-3 (-9 to 3)	-3 (-12 to 13)	-5 (-17 to 7)	

Appetite loss	9 (3 to 15)	1 (-7 to 10)	-1 (-12 to 10)	
Constipation	6 (1 to 10)	2 (-4 to 8)	2 (-6 to 10)	
Diarrhoea	2 (-2 to 5)	-5 (-12 to 2)	-3 (-12 to 6)	
Financial Difficulties	3 (-3 to 8)	2 (-6 to 10)	0 (-11 to 11)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Differences in Quality of Life scores - OES-18 Symptom Scales

End point title	Mean Differences in Quality of Life scores - OES-18 Symptom Scales

End point description:

The mean difference (MD) from Baseline to different timepoints are adjusted by Baseline scores in a linear model. Differences are calculated as Arm B - Arm A.

End point type	Secondary

End point timeframe:

From baseline to different time points (Pre-surgery, 1 year post surgery and 3 years post surgery)

End point values	Pre Surgery	1 year Post Surgery	3 Year Post Surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	332	191	89	
Units: Mean Difference				
number (confidence interval 95%)				
Eating	2 (-3 to 7)	5 (-2 to 12)	6 (-4 to 16)	
Reflux	-1 (-6 to 3)	-4 (-12 to 4)	3 (-10 to 15)	
Pain	4 (1 to 8)	4 (-2 to 10)	2 (-8 to 12)	
Trouble swallowing saliva	-2 (-8 to 3)	-2 (-8 to 4)	2 (-6 to 10)	
Choked when swallowing	-1 (-7 to 6)	-2 (-7 to 3)	4 (-4 to 11)	
Dry mouth	-1 (-7 to 6)	-5 (-13 to 3)	-3 (-16 to 10)	
Trouble with taste	0 (-7 to 7)	-1 (-8 to 6)	3 (-8 to 14)	
Trouble with coughing	6 (1 to 11)	8 (1 to 16)	10 (-1 to 21)	
Trouble talking	0 (-2 to 3)	4 (-2 to 10)	8 (0 to 15)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Differences in Quality of Life scores- OES-18 Functional Scales

End point title	Mean Differences in Quality of Life scores- OES-18 Functional Scales

End point description:

The mean difference (MD) from Baseline to different timepoints are adjusted by Baseline scores in a linear model. Differences are calculated as Arm B - Arm A.

End point type	Secondary

End point timeframe:

From baseline to different time points (Pre-surgery, 1 year post surgery and 3 years post surgery)

End point values	Pre Surgery	1 year Post Surgery	3 Year Post Surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	332	191	89	
Units: Mean Difference				
number (confidence interval 95%)				
Dysphagia	-1 (-6 to 4)	-1 (-8 to 5)	-6 (-15 to 3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted mean differences in Quality of Life scores - QLQ-C30 Global Health Status

End point title	Adjusted mean differences in Quality of Life scores - QLQ-C30 Global Health Status

End point description:

Mean difference (MD) after adjusting by demographics and relevant prognostic factors (age, gender, smoking status and tumour staging)

End point type	Secondary

End point timeframe:

The mean difference (MD) from Baseline to different timepoints (Pre Surgery, 1 year Post Surgery and 3 years Post surgery)

End point values	Pre Surgery	1 year Post Surgery	3 Year Post Surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	332	191	89	
Units: Mean difference				
number (confidence interval 95%)				
Global health status/QoL	-7 (-12 to -3)	-2 (-8 to 4)	-2 (-11 to 7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted mean differences in Quality of Life scores - QLQ-C30 Functional scales

End point title	Adjusted mean differences in Quality of Life scores - QLQ-C30

	Functional scales

End point description:

Mean difference (MD) after adjusting by demographics and relevant prognostic factors (age, gender, smoking status and tumour staging)

End point type	Secondary

End point timeframe:

The mean difference (MD) from Baseline to different timepoints (Pre Surgery, 1 year Post Surgery and 3 years Post surgery)

End point values	Pre Surgery	1 year Post Surgery	3 Year Post Surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	332	191	89	
Units: Mean difference				
number (confidence interval 95%)				
Physical functioning	-4 (-8 to -1)	-4 (-9 to 1)	2 (-7 to 11)	
Role functioning	-5 (-12 to 2)	-3 (-12 to 5)	-4 (-16 to 8)	
Emotional functioning	-4 (-8 to 0)	-6 (-12 to 5)	-1 (-11 to 9)	
Cognitive functioning	0 (-4 to 4)	2 (-5 to 8)	2 (-8 to 12)	
Social functioning	-3 (-9 to 3)	0 (-8 to 8)	3 (-8 to 15)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted mean differences in Quality of Life scores - QLQ-C30 Symptom scales

End point title	Adjusted mean differences in Quality of Life scores - QLQ-C30 Symptom scales

End point description:

Mean difference (MD) after adjusting by demographics and relevant prognostic factors (age, gender, smoking status and tumour staging)

End point type	Secondary

End point timeframe:

The mean difference (MD) from Baseline to different timepoints (Pre Surgery, 1 year Post Surgery and 3 years Post surgery)

End point values	Pre Surgery	1 year Post Surgery	3 Year Post Surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	332	191	89	
Units: Mean difference				
number (confidence interval 95%)				
Fatigue	8 (2 to 13)	-1 (-9 to 6)	-1 (-13 to 11)	
Nausea and vomiting	1 (-2 to 5)	1 (-4 to 6)	0 (-7 to 8)	
Pain	7 (3 to 12)	9 (1 to 17)	3 (-9 to 14)	

Dyspnoea	7 (3 to 12)	6 (-2 to 14)	2 (-11 to 15)	
Insomnia	-3 (-9 to 3)	-3 (-13 to 6)	-4 (-17 to 9)	
Appetite loss	9 (3 to 15)	3 (-5 to 11)	2 (-9 to 13)	
Constipation	5 (0 to 10)	2 (-4 to 8)	5 (-4 to 13)	
Diarrhoea	1 (-2 to 5)	-5 (-12 to 2)	-3 (-13 to 6)	
Financial difficulties	2 (-4 to 8)	1 (-7 to 9)	1 (-11 to 13)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted mean differences in Quality of Life scores - OES Symptom scales

End point title	Adjusted mean differences in Quality of Life scores - OES Symptom scales

End point description:

Mean difference (MD) after adjusting by demographics and relevant prognostic factors (age, gender, smoking status and tumour staging)

End point type	Secondary

End point timeframe:

The mean difference (MD) from Baseline to different timepoints (Pre Surgery, 1 year Post Surgery and 3 years Post surgery)

End point values	Pre Surgery	1 year Post Surgery	3 Year Post Surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	332	191	89	
Units: Mean difference				
number (confidence interval 95%)				
Eating	2 (-3 to 7)	6 (-1 to 13)	5 (-6 to 16)	
Reflux	-2 (-6 to 3)	-4 (-13 to 4)	6 (-7 to 20)	
Pain	4 (0 to 7)	6 (0 to 12)	3 (-8 to 13)	
Trouble swallowing saliva	-3 (-8 to 2)	-3 (-9 to 3)	1 (-8 to 10)	
Choked when swallowing	-1 (-5 to 3)	-2 (-7 to 3)	5 (-3 to 13)	
Dry mouth	-1 (-8 to 5)	-7 (-15 to 2)	-5 (-19 to 9)	
Trouble with taste	0 (-8 to 7)	-1 (-9 to 7)	1 (-10 to 13)	
Trouble with coughing	7 (2 to 12)	8 (1 to 16)	11 (-2 to 23)	
Trouble talking	0 (-2 to 3)	4 (-2 to 11)	6 (-2 to 14)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted mean differences in Quality of Life scores - OES-18 Functional scales

End point title	Adjusted mean differences in Quality of Life scores - OES-18 Functional scales

End point description:

Mean difference (MD) after adjusting by demographics and relevant prognostic factors (age, gender, smoking status and tumour staging)

End point type	Secondary

End point timeframe:

The mean difference (MD) from Baseline to different timepoints (Pre Surgery, 1 year Post Surgery and 3 years Post surgery)

End point values	Pre Surgery	1 year Post Surgery	3 Year Post Surgery	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	332	191	89	
Units: Mean difference				
number (confidence interval 95%)				
Dysphagia	0 (-6 to 5)	-1 (-8 to 6)	-6 (-15 to 3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure (TTF)

End point title	Time to Treatment Failure (TTF)

End point description:

*Due to the differences with respect to the length and nature of the treatments, it was expected that different times to treatment failure would be observed between treatment arms. The analysis presented for OS and DFS provide the key relevant TTF metrics.

End point type	Secondary

End point timeframe:

Time to treatment failure was calculated from randomization to the first of the following events: Discontinuation of therapy, addition of new anti-cancer therapy or recurrence/progression.

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	178		
Units: months				
median (confidence interval 95%)	7.3 (6.8 to 8.2)	22.3 (15.7 to 40.3)		

Statistical analyses

Statistical analysis title	Hazard Ratio (Time to treatment failure)
Comparison groups	Arm A: neoadjuvant and adjuvant chemotherapy v Arm B: neoadjuvant chemoradiation
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Kaplan-Meier
Parameter estimate	Hazard ratio (HR)
Point estimate	1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	2.35

Secondary: Pathological Response

End point title	Pathological Response
End point description:	
Complete pathological response pCR is defined as (y)pT0 or (y)pN0 in pathological staging.	
End point type	Secondary
End point timeframe:	
From randomization to the first of the following events: Discontinuation of therapy, addition of new anti-cancer therapy or recurrence/progression.	

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	167		
Units: Subjects	7	20		

Statistical analyses

Statistical analysis title	Complete Pathological response
Comparison groups	Arm A: neoadjuvant and adjuvant chemotherapy v Arm B: neoadjuvant chemoradiation
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.012
Method	Kaplan-Meier
Parameter estimate	Odds ratio (OR)
Point estimate	0.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.81

Secondary: Complete pathological response adjusted by baseline clinical T and N staging

End point title	Complete pathological response adjusted by baseline clinical T and N staging

End point description:

Multivariate logistic model with pathological complete respoonse (YpT=T0 & pN=N0) adjusted by treatment arm and baseline clinical T and N staging (note that N2 and N3 staging had to be grouped together)

End point type	Secondary

End point timeframe:

From randomization to the first of the following events: Discontinuation of therapy, addition of new anti-cancer therapy or recurrence/progression.

End point values	Intention to treat (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	362			
Units: Odds Ration				
number (confidence interval 95%)				
Regime: Arm A vs Arm B	0.34 (0.13 to 0.79)			
Primary Tumour: T3 vs T2	0.69 (0.27 to 1.98)			
Regional Lymph Nodes: N1 vs N0	0.65 (0.26 to 1.56)			
Regional Lymph Nodes: N2 or N3 vs N0	0.79 (0.21 to 2.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Major pathological response

End point title	Major pathological response

End point description:

From randomization to the first of the following events: Discontinuation of therapy, addition of new anti-cancer therapy or recurrence/progression.

Comprising TRG 1 (complete regression) and TRG 2 (isolated vital residual single tumour cells surrounded by fibrosis) combined.

End point type	Secondary

End point timeframe:

From randomization to the first of the following events: Discontinuation of therapy, addition of new anti-cancer therapy or recurrence/progression.

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	163		
Units: Subjects				
Major Pathological Response (TRG 1 or TRG 2)	19	64		
No Pathological Response (TRG 4 or TRG 5)	100	46		

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour Regression Grade (TRG)

End point title	Tumour Regression Grade (TRG)

End point description:

End point type	Secondary

End point timeframe:

From randomization to the first of the following events: Discontinuation of therapy, addition of new anti-cancer therapy or recurrence/progression.

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	163		
Units: Subjects				
TRG 1	8	23		
TRG 2	11	41		
TRG 3	38	53		
TRG 4	65	39		
TRG 5	35	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Site of Treatment Failure

End point title	Site of Treatment Failure

End point description:

Only Local Regional - Anastomosis, oesophagus, stomach, regional nodes
Only Systemic - Liver, lung, bone, brain, extraregional nodes
Systemic and Local Regional combined

End point type	Secondary

End point timeframe:

Time to treatment failure was calculated from randomization to the first of the following events: Discontinuation of therapy, addition of new anti-cancer therapy or recurrence/progression.

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	178		
Units: Subjects				
Only Local Regional	18	16		
Only Systemic	39	41		
Systemic and Local Regional combined	15	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Pattern of recurrence: Surgical Patients

End point title	Pattern of recurrence: Surgical Patients

End point description:

Pattern of recurrence for surgical patients only

End point type	Secondary

End point timeframe:

Time to treatment failure was calculated from randomization to recurrence

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	167		
Units: Subjects				
Systemic	44	58		

Local Regional	22	28		
Systemic and Local Regional	7	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Response to therapy (endoscopy)

End point title	Response to therapy (endoscopy)

End point description:

Response to therapy as determined by endoscopy

End point type	Secondary

End point timeframe:

From randomization to the first of the following events: Discontinuation of therapy, addition of new anti-cancer therapy or recurrence/progression.

End point values	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	138		
Units: Subjects				
Complete response	23	28		
Partial response	62	83		
No response	45	27		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of informed consent up to 30 days after the the last dose of trial drug has been received.

Adverse event reporting additional description:

AEs graded using National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE)

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Arm A: neoadjuvant and adjuvant chemotherapy

Reporting group description:

Arm A consists of chemotherapy pre-surgery and chemotherapy post-surgery. The chemotherapy regimens included in Neo-Aegis are included as accepted standards of care. Decisions about which chemotherapy regimen to use, i.e. modified MAGIC (ECF/ECX or EOF/EOX) or FLOT, are to be made by the treating clinician.

Reporting group title	Arm B: neoadjuvant chemoradiation

Reporting group description:

Arm B consists of the multimodal CROSS arm, which includes a combination of chemotherapy and radiotherapy prior to surgery. The patient will receive four and a half (4.5) weeks of radiation therapy (41.4 Gy/23 fractions), and 5 weekly cycles of chemotherapy. The chemotherapy and radiotherapy will run concurrently over a 4 and a half-week period. Chemotherapy is given by intravenous infusion on days 1, 8, 15, 22 and 29. The radiation will generally commence on the 1st day of treatment and will run for 4 and a half weeks as follows: days 1-5, days 8-12, days 15-19, days 22-26 and days 29-31 inclusive.

Serious adverse events	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation	
Total subjects affected by serious adverse events			
subjects affected / exposed	91 / 183 (49.73%)	74 / 178 (41.57%)	
number of deaths (all causes)	97	94	
number of deaths resulting from adverse events	10	9	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			

subjects affected / exposed	0 / 183 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Vascular disorders			
Cyanosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flushing			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 183 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphatic fistula			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			

subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	3 / 183 (1.64%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	7 / 183 (3.83%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	6 / 9	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site necrosis			

subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	3 / 183 (1.64%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 183 (2.73%)	10 / 178 (5.62%)	
occurrences causally related to treatment / all	3 / 5	6 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer haemorrhage			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			

subjects affected / exposed	0 / 183 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chylothorax			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 183 (3.28%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	1 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal effusion			

subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	4 / 183 (2.19%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	3 / 183 (1.64%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	10 / 183 (5.46%)	10 / 178 (5.62%)	
occurrences causally related to treatment / all	6 / 10	10 / 12	
deaths causally related to treatment / all	0 / 1	1 / 1	
Pulmonary oedema			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	5 / 183 (2.73%)	6 / 178 (3.37%)	
occurrences causally related to treatment / all	0 / 5	1 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	
Psychiatric disorders			
Aggression			

subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	3 / 183 (1.64%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device leakage			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	0 / 183 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood phosphorus increased			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human metapneumovirus test positive			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutrophil count decreased			
subjects affected / exposed	5 / 183 (2.73%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	6 / 6	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 183 (0.55%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	5 / 183 (2.73%)	6 / 178 (3.37%)	
occurrences causally related to treatment / all	1 / 5	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	3 / 183 (1.64%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	4 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	4 / 183 (2.19%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chemical peritonitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 183 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	

Procedural pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation mucositis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation oesophagitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 183 (0.55%)	5 / 178 (2.81%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pericarditis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular dysfunction			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 183 (0.55%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Autonomic neuropathy			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dizziness			

subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculitis brachial			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 183 (0.55%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	6 / 183 (3.28%)	6 / 178 (3.37%)	
occurrences causally related to treatment / all	6 / 6	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 183 (1.64%)	4 / 178 (2.25%)	
occurrences causally related to treatment / all	3 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 183 (2.19%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 183 (0.55%)	4 / 178 (2.25%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	4 / 183 (2.19%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic hernia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	17 / 183 (9.29%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	17 / 19	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	11 / 183 (6.01%)	9 / 178 (5.06%)	
occurrences causally related to treatment / all	0 / 14	5 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric fistula			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	0 / 183 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hiatus hernia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal infarction			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	11 / 183 (6.01%)	11 / 178 (6.18%)	
occurrences causally related to treatment / all	10 / 13	10 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	8 / 183 (4.37%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	9 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal fistula			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal food impaction			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal pain			

subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 183 (0.00%)	9 / 178 (5.06%)	
occurrences causally related to treatment / all	0 / 0	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Regurgitation			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	21 / 183 (11.48%)	6 / 178 (3.37%)	
occurrences causally related to treatment / all	18 / 22	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash erythematous			

subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	3 / 183 (1.64%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 183 (1.64%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	3 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			

subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	4 / 183 (2.19%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	4 / 183 (2.19%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 183 (2.19%)	5 / 178 (2.81%)	
occurrences causally related to treatment / all	0 / 4	3 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	3 / 183 (1.64%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Stoma site infection			

subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected COVID-19			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 183 (0.00%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	5 / 183 (2.73%)	5 / 178 (2.81%)	
occurrences causally related to treatment / all	3 / 5	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	6 / 183 (3.28%)	11 / 178 (6.18%)	
occurrences causally related to treatment / all	6 / 6	8 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	3 / 183 (1.64%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			

subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A: neoadjuvant and adjuvant chemotherapy	Arm B: neoadjuvant chemoradiation	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	182 / 183 (99.45%)	177 / 178 (99.44%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Tumour pain			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Deep vein thrombosis			
subjects affected / exposed	1 / 183 (0.55%)	2 / 178 (1.12%)	
occurrences (all)	1	2	
Embolism			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Flushing			
subjects affected / exposed	1 / 183 (0.55%)	3 / 178 (1.69%)	
occurrences (all)	1	3	
Hot flush			
subjects affected / exposed	1 / 183 (0.55%)	2 / 178 (1.12%)	
occurrences (all)	1	2	
Hypertension			

subjects affected / exposed	9 / 183 (4.92%)	3 / 178 (1.69%)	
occurrences (all)	9	4	
Hypotension			
subjects affected / exposed	5 / 183 (2.73%)	11 / 178 (6.18%)	
occurrences (all)	6	12	
Orthostatic hypotension			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Phlebitis			
subjects affected / exposed	5 / 183 (2.73%)	0 / 178 (0.00%)	
occurrences (all)	5	0	
Thrombophlebitis			
subjects affected / exposed	5 / 183 (2.73%)	2 / 178 (1.12%)	
occurrences (all)	6	2	
Thrombosis			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Vascular pain			
subjects affected / exposed	4 / 183 (2.19%)	0 / 178 (0.00%)	
occurrences (all)	4	0	
General disorders and administration site conditions			
Administration site extravasation			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Administration site inflammation			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Administration site pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Asthenia			
subjects affected / exposed	7 / 183 (3.83%)	3 / 178 (1.69%)	
occurrences (all)	11	4	
Catheter site pain			

subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Chest discomfort			
subjects affected / exposed	1 / 183 (0.55%)	3 / 178 (1.69%)	
occurrences (all)	1	3	
Chest pain			
subjects affected / exposed	12 / 183 (6.56%)	9 / 178 (5.06%)	
occurrences (all)	13	14	
Chills			
subjects affected / exposed	2 / 183 (1.09%)	2 / 178 (1.12%)	
occurrences (all)	3	2	
Complication associated with device			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Extravasation			
subjects affected / exposed	2 / 183 (1.09%)	1 / 178 (0.56%)	
occurrences (all)	2	1	
Fatigue			
subjects affected / exposed	117 / 183 (63.93%)	103 / 178 (57.87%)	
occurrences (all)	215	155	
Feeling hot			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Hernia			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Induration			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	0 / 183 (0.00%)	3 / 178 (1.69%)	
occurrences (all)	0	3	
Malaise			
subjects affected / exposed	2 / 183 (1.09%)	1 / 178 (0.56%)	
occurrences (all)	2	2	
Mucosal dryness			

subjects affected / exposed	3 / 183 (1.64%)	0 / 178 (0.00%)	
occurrences (all)	3	0	
Mucosal inflammation			
subjects affected / exposed	27 / 183 (14.75%)	15 / 178 (8.43%)	
occurrences (all)	43	17	
Non-cardiac chest pain			
subjects affected / exposed	1 / 183 (0.55%)	4 / 178 (2.25%)	
occurrences (all)	1	4	
Oedema peripheral			
subjects affected / exposed	6 / 183 (3.28%)	2 / 178 (1.12%)	
occurrences (all)	8	2	
Pain			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Peripheral swelling			
subjects affected / exposed	5 / 183 (2.73%)	1 / 178 (0.56%)	
occurrences (all)	5	2	
Pyrexia			
subjects affected / exposed	8 / 183 (4.37%)	18 / 178 (10.11%)	
occurrences (all)	8	20	
Secretion discharge			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Sensation of foreign body			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Swelling			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Temperature intolerance			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Ulcer haemorrhage			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Immune system disorders			

Cytokine release syndrome			
subjects affected / exposed	0 / 183 (0.00%)	2 / 178 (1.12%)	
occurrences (all)	0	5	
Drug hypersensitivity			
subjects affected / exposed	2 / 183 (1.09%)	5 / 178 (2.81%)	
occurrences (all)	2	6	
Hypersensitivity			
subjects affected / exposed	1 / 183 (0.55%)	8 / 178 (4.49%)	
occurrences (all)	1	10	
Seasonal allergy			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Breast pain			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Pelvic pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Penile pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Atelectasis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	36 / 183 (19.67%)	48 / 178 (26.97%)	
occurrences (all)	39	58	
Dysaesthesia pharynx			

subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Dysphonia			
subjects affected / exposed	3 / 183 (1.64%)	2 / 178 (1.12%)	
occurrences (all)	3	2	
Dyspnoea			
subjects affected / exposed	27 / 183 (14.75%)	26 / 178 (14.61%)	
occurrences (all)	35	32	
Dyspnoea exertional			
subjects affected / exposed	2 / 183 (1.09%)	2 / 178 (1.12%)	
occurrences (all)	2	2	
Epistaxis			
subjects affected / exposed	8 / 183 (4.37%)	14 / 178 (7.87%)	
occurrences (all)	8	15	
Haemoptysis			
subjects affected / exposed	1 / 183 (0.55%)	2 / 178 (1.12%)	
occurrences (all)	1	2	
Hiccups			
subjects affected / exposed	12 / 183 (6.56%)	10 / 178 (5.62%)	
occurrences (all)	20	17	
Hypoxia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Increased viscosity of upper respiratory secretion			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Laryngospasm			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	3	0	
Nasal congestion			
subjects affected / exposed	2 / 183 (1.09%)	1 / 178 (0.56%)	
occurrences (all)	2	1	
Nasal discomfort			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	

Oropharyngeal pain			
subjects affected / exposed	9 / 183 (4.92%)	6 / 178 (3.37%)	
occurrences (all)	10	7	
Oropharyngeal spasm			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	3 / 183 (1.64%)	2 / 178 (1.12%)	
occurrences (all)	3	2	
Pleuritic pain			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Pneumonitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Pneumothorax			
subjects affected / exposed	3 / 183 (1.64%)	0 / 178 (0.00%)	
occurrences (all)	3	0	
Productive cough			
subjects affected / exposed	8 / 183 (4.37%)	5 / 178 (2.81%)	
occurrences (all)	8	5	
Pulmonary embolism			
subjects affected / exposed	3 / 183 (1.64%)	2 / 178 (1.12%)	
occurrences (all)	3	2	
Pulmonary fibrosis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Respiratory failure			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	4 / 183 (2.19%)	0 / 178 (0.00%)	
occurrences (all)	4	0	
Sinus pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	

Tachypnoea			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Throat irritation			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Upper-airway cough syndrome			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	2	
Anger			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	6 / 183 (3.28%)	2 / 178 (1.12%)	
occurrences (all)	6	3	
Confusional state			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Depressed mood			
subjects affected / exposed	2 / 183 (1.09%)	3 / 178 (1.69%)	
occurrences (all)	2	3	
Depression			
subjects affected / exposed	1 / 183 (0.55%)	2 / 178 (1.12%)	
occurrences (all)	1	2	
Hallucination			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Insomnia			

subjects affected / exposed	13 / 183 (7.10%)	21 / 178 (11.80%)	
occurrences (all)	13	26	
Suicidal ideation			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	15 / 183 (8.20%)	4 / 178 (2.25%)	
occurrences (all)	18	4	
Amylase increased			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 183 (4.92%)	5 / 178 (2.81%)	
occurrences (all)	9	6	
Blood albumin decreased			
subjects affected / exposed	3 / 183 (1.64%)	2 / 178 (1.12%)	
occurrences (all)	4	4	
Blood alkaline phosphatase decreased			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	11 / 183 (6.01%)	0 / 178 (0.00%)	
occurrences (all)	13	0	
Blood bicarbonate decreased			
subjects affected / exposed	1 / 183 (0.55%)	6 / 178 (3.37%)	
occurrences (all)	1	6	
Blood bicarbonate increased			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Blood bilirubin increased			

subjects affected / exposed	3 / 183 (1.64%)	5 / 178 (2.81%)		
occurrences (all)	3	7		
Blood calcium decreased				
subjects affected / exposed	1 / 183 (0.55%)	3 / 178 (1.69%)		
occurrences (all)	1	3		
Blood calcium increased				
subjects affected / exposed	0 / 183 (0.00%)	2 / 178 (1.12%)		
occurrences (all)	0	3		
Blood chloride decreased				
subjects affected / exposed	0 / 183 (0.00%)	3 / 178 (1.69%)		
occurrences (all)	0	3		
Blood chloride increased				
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)		
occurrences (all)	1	0		
Blood cholesterol increased				
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)		
occurrences (all)	1	0		
Blood creatinine decreased				
subjects affected / exposed	1 / 183 (0.55%)	3 / 178 (1.69%)		
occurrences (all)	1	5		
Blood creatine increased				
subjects affected / exposed	6 / 183 (3.28%)	4 / 178 (2.25%)		
occurrences (all)	9	6		
Blood folate decreased				
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)		
occurrences (all)	0	1		
Blood glucose decreased				
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)		
occurrences (all)	0	1		
Blood glucagon increased				
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)		
occurrences (all)	1	0		
Blood lactate dehydrogenase increased				
subjects affected / exposed	5 / 183 (2.73%)	3 / 178 (1.69%)		
occurrences (all)	6	3		

Blood magnesium decreased				
subjects affected / exposed	5 / 183 (2.73%)	4 / 178 (2.25%)		
occurrences (all)	6	5		
Blood parathyroid hormone increased				
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)		
occurrences (all)	0	1		
Blood phosphorus decreased				
subjects affected / exposed	10 / 183 (5.46%)	0 / 178 (0.00%)		
occurrences (all)	11	0		
Blood potassium decreased				
subjects affected / exposed	4 / 183 (2.19%)	3 / 178 (1.69%)		
occurrences (all)	4	3		
Blood potassium increased				
subjects affected / exposed	0 / 183 (0.00%)	3 / 178 (1.69%)		
occurrences (all)	0	3		
Blood sodium decreased				
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)		
occurrences (all)	1	0		
Blood urea increased				
subjects affected / exposed	3 / 183 (1.64%)	5 / 178 (2.81%)		
occurrences (all)	3	5		
Blood uric acid decreased				
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)		
occurrences (all)	0	1		
Blood uric acid increased				
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)		
occurrences (all)	2	0		
Body temperature increased				
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)		
occurrences (all)	0	2		
C-reactive protein increased				
subjects affected / exposed	2 / 183 (1.09%)	1 / 178 (0.56%)		
occurrences (all)	4	1		
Creatinine renal clearance decreased				

subjects affected / exposed	3 / 183 (1.64%)	0 / 178 (0.00%)	
occurrences (all)	3	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Full blood count abnormal			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 183 (0.55%)	4 / 178 (2.25%)	
occurrences (all)	1	6	
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Haemoglobin decreased			
subjects affected / exposed	26 / 183 (14.21%)	5 / 178 (2.81%)	
occurrences (all)	62	8	
Heart rate irregular			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
International normalised ratio increased			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Liver function test abnormal			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Lymphocyte count decreased			
subjects affected / exposed	0 / 183 (0.00%)	8 / 178 (4.49%)	
occurrences (all)	0	28	
Neutrophil count decreased			
subjects affected / exposed	66 / 183 (36.07%)	15 / 178 (8.43%)	
occurrences (all)	150	23	
Neutrophil count increased			

subjects affected / exposed	4 / 183 (2.19%)	3 / 178 (1.69%)	
occurrences (all)	4	3	
Oxygen saturation decreased			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	16 / 183 (8.74%)	17 / 178 (9.55%)	
occurrences (all)	25	20	
Prothrombin time prolonged			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Serum ferritin decreased			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	59 / 183 (32.24%)	30 / 178 (16.85%)	
occurrences (all)	75	36	
White blood cell count decreased			
subjects affected / exposed	28 / 183 (15.30%)	19 / 178 (10.67%)	
occurrences (all)	62	31	
White blood cell count increased			
subjects affected / exposed	4 / 183 (2.19%)	3 / 178 (1.69%)	
occurrences (all)	4	3	
White blood cells urine			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	2 / 183 (1.09%)	1 / 178 (0.56%)	
occurrences (all)	2	1	
Fall			

subjects affected / exposed	2 / 183 (1.09%)	1 / 178 (0.56%)	
occurrences (all)	2	1	
Foot fracture			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Gastrointestinal anastomotic stenosis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Head injury			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Incisional hernia			
subjects affected / exposed	2 / 183 (1.09%)	1 / 178 (0.56%)	
occurrences (all)	2	1	
Nerve injury			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Post procedural erythema			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Postoperative wound complication			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	9 / 183 (4.92%)	4 / 178 (2.25%)	
occurrences (all)	11	5	
Radiation mucositis			
subjects affected / exposed	0 / 183 (0.00%)	2 / 178 (1.12%)	
occurrences (all)	0	2	
Radiation oesophagitis			
subjects affected / exposed	0 / 183 (0.00%)	2 / 178 (1.12%)	
occurrences (all)	0	3	
Radiation skin injury			
subjects affected / exposed	0 / 183 (0.00%)	5 / 178 (2.81%)	
occurrences (all)	0	5	
Rib fracture			

subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Splenic rupture			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Stoma site erythema			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Superficial injury of eye			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Wound complication			
subjects affected / exposed	3 / 183 (1.64%)	0 / 178 (0.00%)	
occurrences (all)	3	0	
Wrist fracture			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Arteriospasm coronary			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation			
subjects affected / exposed	5 / 183 (2.73%)	1 / 178 (0.56%)	
occurrences (all)	5	1	
Atrial flutter			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Atrioventricular block first degree			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Cardiac disorder			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	

Myocardial infarction			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	2	
Pericarditis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Sinus bradycardia			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Sinus tachycardia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	3 / 183 (1.64%)	5 / 178 (2.81%)	
occurrences (all)	3	5	
Ventricular extrasystoles			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Ageusia			
subjects affected / exposed	3 / 183 (1.64%)	3 / 178 (1.69%)	
occurrences (all)	3	3	
Akathisia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Anaesthesia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Aphasia			
subjects affected / exposed	0 / 183 (0.00%)	2 / 178 (1.12%)	
occurrences (all)	0	2	
Cognitive disorder			

subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Cold dysaesthesia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Disturbance in attention			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	17 / 183 (9.29%)	11 / 178 (6.18%)	
occurrences (all)	18	11	
Dysaesthesia			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	3	0	
Dysgeusia			
subjects affected / exposed	8 / 183 (4.37%)	8 / 178 (4.49%)	
occurrences (all)	11	8	
Dyspraxia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	10 / 183 (5.46%)	14 / 178 (7.87%)	
occurrences (all)	12	18	
Hypoaesthesia			
subjects affected / exposed	3 / 183 (1.64%)	2 / 178 (1.12%)	
occurrences (all)	3	2	
Lethargy			
subjects affected / exposed	8 / 183 (4.37%)	5 / 178 (2.81%)	
occurrences (all)	10	5	
Nerve compression			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Neuralgia			
subjects affected / exposed	2 / 183 (1.09%)	2 / 178 (1.12%)	
occurrences (all)	2	2	
Neuropathy peripheral			

subjects affected / exposed	69 / 183 (37.70%)	13 / 178 (7.30%)	
occurrences (all)	115	15	
Paraesthesia			
subjects affected / exposed	9 / 183 (4.92%)	3 / 178 (1.69%)	
occurrences (all)	11	3	
Parosmia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Peripheral sensory neuropathy			
subjects affected / exposed	13 / 183 (7.10%)	0 / 178 (0.00%)	
occurrences (all)	26	0	
Peroneal nerve palsy			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Presyncope			
subjects affected / exposed	4 / 183 (2.19%)	2 / 178 (1.12%)	
occurrences (all)	4	2	
Radiculitis brachial			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Restless legs syndrome			
subjects affected / exposed	0 / 183 (0.00%)	2 / 178 (1.12%)	
occurrences (all)	0	2	
Syncope			
subjects affected / exposed	6 / 183 (3.28%)	2 / 178 (1.12%)	
occurrences (all)	6	3	
Taste disorder			
subjects affected / exposed	13 / 183 (7.10%)	6 / 178 (3.37%)	
occurrences (all)	13	7	
Tremor			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Vocal cord paralysis			

subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	25 / 183 (13.66%)	8 / 178 (4.49%)	
occurrences (all)	35	9	
Febrile neutropenia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			
subjects affected / exposed	0 / 183 (0.00%)	3 / 178 (1.69%)	
occurrences (all)	0	3	
Myelosuppression			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	43 / 183 (23.50%)	13 / 178 (7.30%)	
occurrences (all)	65	18	
Thrombocytopenia			
subjects affected / exposed	3 / 183 (1.64%)	1 / 178 (0.56%)	
occurrences (all)	5	1	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Hypoacusis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Tinnitus			

subjects affected / exposed	6 / 183 (3.28%)	1 / 178 (0.56%)	
occurrences (all)	8	1	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Conjunctival haemorrhage			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	6 / 183 (3.28%)	0 / 178 (0.00%)	
occurrences (all)	6	0	
Eye discharge			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Foreign body sensation in eyes			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	6 / 183 (3.28%)	0 / 178 (0.00%)	
occurrences (all)	7	0	
Ocular hyperaemia			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Vision blurred			
subjects affected / exposed	3 / 183 (1.64%)	1 / 178 (0.56%)	
occurrences (all)	6	1	
Visual impairment			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 183 (1.09%)	3 / 178 (1.69%)	
occurrences (all)	2	3	
Abdominal distension			

subjects affected / exposed	1 / 183 (0.55%)	6 / 178 (3.37%)	
occurrences (all)	1	8	
Abdominal pain			
subjects affected / exposed	29 / 183 (15.85%)	9 / 178 (5.06%)	
occurrences (all)	39	10	
Abdominal pain lower			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	11 / 183 (6.01%)	19 / 178 (10.67%)	
occurrences (all)	15	25	
Abdominal rigidity			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Abdominal tenderness			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Anal fissure			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Anal haemorrhage			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Aphthous ulcer			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Colitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	71 / 183 (38.80%)	78 / 178 (43.82%)	
occurrences (all)	103	102	
Diaphragmatic hernia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			

subjects affected / exposed	93 / 183 (50.82%)	43 / 178 (24.16%)	
occurrences (all)	176	60	
Dry mouth			
subjects affected / exposed	5 / 183 (2.73%)	6 / 178 (3.37%)	
occurrences (all)	10	6	
Dumping syndrome			
subjects affected / exposed	8 / 183 (4.37%)	3 / 178 (1.69%)	
occurrences (all)	8	3	
Dyspepsia			
subjects affected / exposed	16 / 183 (8.74%)	16 / 178 (8.99%)	
occurrences (all)	22	19	
Dysphagia			
subjects affected / exposed	35 / 183 (19.13%)	44 / 178 (24.72%)	
occurrences (all)	44	55	
Enterocolitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Epigastric discomfort			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Eructation			
subjects affected / exposed	1 / 183 (0.55%)	3 / 178 (1.69%)	
occurrences (all)	1	5	
Faecaloma			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Faeces soft			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	2 / 183 (1.09%)	3 / 178 (1.69%)	
occurrences (all)	2	3	
Gastritis			
subjects affected / exposed	0 / 183 (0.00%)	6 / 178 (3.37%)	
occurrences (all)	0	10	
Gastrooesophageal reflux disease			

subjects affected / exposed	20 / 183 (10.93%)	29 / 178 (16.29%)	
occurrences (all)	24	33	
Glossitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Haematemesis			
subjects affected / exposed	3 / 183 (1.64%)	0 / 178 (0.00%)	
occurrences (all)	3	0	
Haemorrhoids			
subjects affected / exposed	3 / 183 (1.64%)	3 / 178 (1.69%)	
occurrences (all)	3	3	
Intestinal obstruction			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Lip pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Melaena			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	6 / 183 (3.28%)	0 / 178 (0.00%)	
occurrences (all)	7	0	
Nausea			
subjects affected / exposed	110 / 183 (60.11%)	101 / 178 (56.74%)	
occurrences (all)	210	143	
Obstruction gastric			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Odynophagia			
subjects affected / exposed	5 / 183 (2.73%)	38 / 178 (21.35%)	
occurrences (all)	5	44	
Oesophageal food impaction			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Oesophageal hypomotility			

subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Oesophageal pain			
subjects affected / exposed	1 / 183 (0.55%)	11 / 178 (6.18%)	
occurrences (all)	1	14	
Oesophageal perforation			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Oesophageal stenosis			
subjects affected / exposed	1 / 183 (0.55%)	2 / 178 (1.12%)	
occurrences (all)	1	2	
Oesophagitis			
subjects affected / exposed	6 / 183 (3.28%)	56 / 178 (31.46%)	
occurrences (all)	7	72	
Oral dysaesthesia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	5 / 183 (2.73%)	2 / 178 (1.12%)	
occurrences (all)	5	2	
Overflow diarrhoea			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Pancreatic failure			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Peptic ulcer			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Rectal haemorrhage			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Regurgitation			
subjects affected / exposed	3 / 183 (1.64%)	1 / 178 (0.56%)	
occurrences (all)	3	1	
Retching			

subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Salivary hypersecretion			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Steatorrhoea			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	7 / 183 (3.83%)	7 / 178 (3.93%)	
occurrences (all)	10	7	
Tongue blistering			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	1 / 183 (0.55%)	2 / 178 (1.12%)	
occurrences (all)	1	2	
Upper gastrointestinal perforation			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	52 / 183 (28.42%)	35 / 178 (19.66%)	
occurrences (all)	79	46	
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Hepatic function abnormal			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	47 / 183 (25.68%)	15 / 178 (8.43%)	
occurrences (all)	57	15	
Blister			

subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Cold sweat			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	1 / 183 (0.55%)	5 / 178 (2.81%)	
occurrences (all)	1	5	
Dermatitis acneiform			
subjects affected / exposed	0 / 183 (0.00%)	3 / 178 (1.69%)	
occurrences (all)	0	5	
Dry skin			
subjects affected / exposed	6 / 183 (3.28%)	2 / 178 (1.12%)	
occurrences (all)	8	2	
Eczema			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	2 / 183 (1.09%)	5 / 178 (2.81%)	
occurrences (all)	2	5	
Hyperhidrosis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Nail disorder			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Nail toxicity			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	3 / 183 (1.64%)	0 / 178 (0.00%)	
occurrences (all)	4	0	
Palmar erythema			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	3	0	
Palmar-plantar erythrodysaesthesia			

syndrome			
subjects affected / exposed	25 / 183 (13.66%)	3 / 178 (1.69%)	
occurrences (all)	31	3	
Pigmentation disorder			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 183 (0.55%)	3 / 178 (1.69%)	
occurrences (all)	1	4	
Rash			
subjects affected / exposed	10 / 183 (5.46%)	10 / 178 (5.62%)	
occurrences (all)	12	11	
Rash maculo-papular			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Rash papular			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Rosacea			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Scar pain			
subjects affected / exposed	7 / 183 (3.83%)	1 / 178 (0.56%)	
occurrences (all)	8	1	
Skin disorder			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Skin exfoliation			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Skin fissures			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Skin reaction			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	

Skin texture abnormal			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Subcutaneous emphysema			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Dysuria			
subjects affected / exposed	3 / 183 (1.64%)	3 / 178 (1.69%)	
occurrences (all)	3	3	
Haematuria			
subjects affected / exposed	0 / 183 (0.00%)	2 / 178 (1.12%)	
occurrences (all)	0	2	
Nocturia			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Pollakiuria			
subjects affected / exposed	3 / 183 (1.64%)	4 / 178 (2.25%)	
occurrences (all)	3	4	
Renal vein thrombosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Urinary hesitation			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Urinary retention			

subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 183 (6.01%)	7 / 178 (3.93%)	
occurrences (all)	11	8	
Arthritis			
subjects affected / exposed	2 / 183 (1.09%)	1 / 178 (0.56%)	
occurrences (all)	2	1	
Back pain			
subjects affected / exposed	9 / 183 (4.92%)	8 / 178 (4.49%)	
occurrences (all)	9	9	
Flank pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Groin pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Joint swelling			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Muscle spasms			
subjects affected / exposed	6 / 183 (3.28%)	2 / 178 (1.12%)	
occurrences (all)	6	2	
Muscular weakness			
subjects affected / exposed	3 / 183 (1.64%)	2 / 178 (1.12%)	
occurrences (all)	3	2	
Musculoskeletal chest pain			
subjects affected / exposed	4 / 183 (2.19%)	3 / 178 (1.69%)	
occurrences (all)	4	4	
Musculoskeletal discomfort			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Musculoskeletal pain			

subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	3 / 183 (1.64%)	1 / 178 (0.56%)	
occurrences (all)	3	1	
Neck pain			
subjects affected / exposed	1 / 183 (0.55%)	2 / 178 (1.12%)	
occurrences (all)	1	2	
Osteopenia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	13 / 183 (7.10%)	2 / 178 (1.12%)	
occurrences (all)	14	4	
Pain in jaw			
subjects affected / exposed	3 / 183 (1.64%)	0 / 178 (0.00%)	
occurrences (all)	4	0	
Rhabdomyolysis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Spinal osteoarthritis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Trismus			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Candida infection			
subjects affected / exposed	2 / 183 (1.09%)	1 / 178 (0.56%)	
occurrences (all)	2	1	

Cellulitis			
subjects affected / exposed	2 / 183 (1.09%)	2 / 178 (1.12%)	
occurrences (all)	2	2	
Conjunctivitis			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Cystitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Diverticulitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Erysipelas			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Folliculitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Fungal infection			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Haemophilus infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	2 / 183 (1.09%)	3 / 178 (1.69%)	
occurrences (all)	2	3	
Infected dermal cyst			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	

Infection			
subjects affected / exposed	2 / 183 (1.09%)	3 / 178 (1.69%)	
occurrences (all)	2	3	
Influenza			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Lip infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Localised infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	6 / 183 (3.28%)	7 / 178 (3.93%)	
occurrences (all)	6	7	
Mucosal infection			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	2	0	
Nail infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Oral candidiasis			
subjects affected / exposed	6 / 183 (3.28%)	13 / 178 (7.30%)	
occurrences (all)	6	14	
Oral herpes			
subjects affected / exposed	2 / 183 (1.09%)	1 / 178 (0.56%)	
occurrences (all)	2	1	
Oral infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	

Pneumonia			
subjects affected / exposed	2 / 183 (1.09%)	3 / 178 (1.69%)	
occurrences (all)	2	4	
Pneumonia aspiration			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Post procedural infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Postoperative wound infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	2 / 183 (1.09%)	1 / 178 (0.56%)	
occurrences (all)	2	1	
Sepsis			
subjects affected / exposed	2 / 183 (1.09%)	1 / 178 (0.56%)	
occurrences (all)	2	1	
Sinusitis			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Skin infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Staphylococcal infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Stoma site infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	2	0	

Upper respiratory tract infection			
subjects affected / exposed	2 / 183 (1.09%)	2 / 178 (1.12%)	
occurrences (all)	2	3	
Urinary tract infection			
subjects affected / exposed	5 / 183 (2.73%)	5 / 178 (2.81%)	
occurrences (all)	6	6	
Viral infection			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Wound infection			
subjects affected / exposed	3 / 183 (1.64%)	1 / 178 (0.56%)	
occurrences (all)	3	1	
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	2 / 183 (1.09%)	1 / 178 (0.56%)	
occurrences (all)	2	1	
Decreased appetite			
subjects affected / exposed	54 / 183 (29.51%)	53 / 178 (29.78%)	
occurrences (all)	72	70	
Dehydration			
subjects affected / exposed	3 / 183 (1.64%)	0 / 178 (0.00%)	
occurrences (all)	3	0	
Electrolyte imbalance			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Gout			
subjects affected / exposed	3 / 183 (1.64%)	2 / 178 (1.12%)	
occurrences (all)	4	3	
Hypercalcaemia			
subjects affected / exposed	6 / 183 (3.28%)	0 / 178 (0.00%)	
occurrences (all)	7	0	
Hyperglycaemia			

subjects affected / exposed	4 / 183 (2.19%)	1 / 178 (0.56%)	
occurrences (all)	4	1	
Hyperkalaemia			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	3	
Hypermagnesaemia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Hypernatraemia			
subjects affected / exposed	2 / 183 (1.09%)	0 / 178 (0.00%)	
occurrences (all)	6	0	
Hyperphosphataemia			
subjects affected / exposed	1 / 183 (0.55%)	1 / 178 (0.56%)	
occurrences (all)	1	1	
Hypoalbuminaemia			
subjects affected / exposed	16 / 183 (8.74%)	2 / 178 (1.12%)	
occurrences (all)	34	5	
Hypocalcaemia			
subjects affected / exposed	15 / 183 (8.20%)	3 / 178 (1.69%)	
occurrences (all)	27	4	
Hypoglycaemia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	21 / 183 (11.48%)	7 / 178 (3.93%)	
occurrences (all)	32	10	
Hypomagnesaemia			
subjects affected / exposed	17 / 183 (9.29%)	6 / 178 (3.37%)	
occurrences (all)	28	8	
Hyponatraemia			
subjects affected / exposed	10 / 183 (5.46%)	4 / 178 (2.25%)	
occurrences (all)	13	4	
Hypophosphataemia			
subjects affected / exposed	19 / 183 (10.38%)	12 / 178 (6.74%)	
occurrences (all)	40	16	
Iron deficiency			

subjects affected / exposed	1 / 183 (0.55%)	0 / 178 (0.00%)	
occurrences (all)	1	0	
Malnutrition			
subjects affected / exposed	0 / 183 (0.00%)	1 / 178 (0.56%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2011	Protocol Amendment to Protocol v2 included editorial and admin changes as well as Therapy changes. Update to patient information leaflet also included.
19 June 2012	Update to Protocol version 3 and updates to patient information leaflets.
21 January 2014	Update to Protocol v 4, included updates to Study assessments and procedures. Also included updates to Patient information leaflets and schedule of treatments.
27 January 2015	Update to Protocol version 5 included updates to sample size, recruitment period, eligibility criteria, therapy changes and administrative changes.
10 March 2015	Update to protocol to version 6 included update requested by the MHRA in UK. Version 6 was applicable to UK only
26 February 2016	Update to Protocol version 8, included updated guidance on live vaccinations, inclusion criteria and contraceptive requirements.
28 April 2017	Update to Protocol version 9 included updates to inclusion and exclusion criteria, adverse event guidance and timeframes for screening and treatment assessments.
22 May 2018	Update to Protocol version 10.2 included update to therapy by permitting the addition of FLOT regimen as an alternative to MAGIC regimen for neoadjuvant and adjuvant chemotherapy in the study. Other updates to therapy and exclusion criteria also included.
11 June 2019	Update to Protocol 11 included updates to therapy, sample size, statistical considerations and study assessments and procedures.
27 October 2020	Update to Protocol version 12 included update to duration of follow-up period, safety information, the translational sub-study and other administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 March 2020	Temporary Halt to recruitment due to the COVID-19 pandemic	13 August 2020

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study was under powered due to early termination (70% of planned patients). At 2nd futility analysis (50% of deaths) DSMB assessed, that futility was not evident but data was unlikely to change with increased numbers and longer-term follow up.

Notes: