Clinical trial results:
Multicenter, explorative phase II study of perioperative 5-FU, leucovorin, docetaxel, and oxaliplatin (FLOT) in combination with Trastuzumab in patients with HER2-positive, locally advanced resectable adenocarcinoma of the gastroesophageal junction or stomach (HerFLOT)

Summary

EudraCT number	2011-001507-13
Trial protocol	DE
Global end of trial date	28 February 2017

Results information

Result version number	v1 (current)
This version publication date	16 September 2021
First version publication date	16 September 2021

Trial information

Trial identification

Sponsor protocol code	AIO-STO-0310

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01472029
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AIO-Studien-gGmbH
Sponsor organisation address	Kuno-Fischer-Str. 8, Berlin, Germany, 14057
Public contact	info@aio-studien-ggmbh.de, AIO-Studien-gGmbH, info@aio-studien-ggmbh.de
Scientific contact	info@aio-studien-ggmbh.de, AIO-Studien-gGmbH, info@aio-studien-ggmbh.de

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	28 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2017
Global end of trial reached?	Yes
Global end of trial date	28 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective of the study was to estimate the efficacy of the trastuzumab/FLOT combination consisting of 5-FU/leucovorin, oxaliplatin, docetaxel and the antibody in locoregional cancer of the stomach or gastroesophageal junction, based on the rate of complete pathological responses (percentage of patients with pCR referring to the total number of enrolled and eligible patients), as evaluated centrally by a reference pathologists.

Protection of trial subjects:

This study was planned, analyzed and conducted according to the study protocol and in accordance with the International Conference on Harmonization (ICH) ‚Guideline for Good Clinical Practice E6(R1)‘, CPMP/ICH/135/95, based on the principles of the Declaration of Helsinki (1964) and its October 1996 amendment (Somerset West, South Africa). The study was duly conducted in compliance with the German Arzneimittelgesetz (AMG; German Drug Law), and the corresponding Directive 2001/20/EC. Subjects were fully informed regarding all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2011
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	Germany: 58
Worldwide total number of subjects	58
EEA total number of subjects	58

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)	35
From 65 to 84 years	22
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled between January 2012 and July 2013.

Pre-assignment

Screening details:

Since only patients with HER2-positive tumors were to be enrolled, 265 patients were planned to be screened. However, only 95 patients had to be acutally screened in order to enroll 58 HER2-positive patients into the main study.

Period 1

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

Arms

Arm title	Overall trial

Arm description: -

Arm type	Experimental
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Per protocol: 24h infusion at 2600 mg/m2.

About half of the patient received the total number of medical treatment cycles as scheduled according to the study protocol. The overall mean relative dose intensity, based on cycles actually administered, amounted to 94% for 5-fluorouracil.

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

Dosage and administration details:

Per protocol: 1h infusion at 200mg/m2

About half of the patient received the total number of medical treatment cycles as scheduled according to the study protocol. The overall mean relative dose intensity, based on cycles actually administered, amounted to 97% for folinic acid.

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

Dosage and administration details:

Per protocol: 2h infustion at 50mg/m2

About half of the patient received the total number of medical treatment cycles as scheduled according to the study protocol. The overall mean relative dose intensity, based on cycles actually administered, amounted to 91% for docetaxel.

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

Dosage and administration details:

Per protocol: 2h infusion at 85mg/m2

About half of the patient received the total number of medical treatment cycles as scheduled according to the study protocol. The overall mean relative dose intensity, based on cycles actually administered, amounted to 94% for oxaliplatin.

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

Dosage and administration details:

Per protocol: 1h infusion at 4mg/kg; 6mg/kg loading dose at first administration.

About half of the patient received the total number of medical treatment cycles as scheduled according to the study protocol. The overall mean relative dose intensity, based on cycles actually administered, amounted to 99% for trastuzumab.

Number of subjects in period 1	Overall trial
Started	58
Completed	56
Not completed	2
Protocol deviation	2

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	58	58	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	62		
full range (min-max)	32 to 86	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	42	42	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Two of the enrolled patients were excluded from the full analysis set due to major violations of in- and exclusion criteria. In one case, the finding peritoneal carcinomatosis led to the retrospective exclusion of the patient from the FAS. In the other case, exclusion from the FAS was due to the retrospective finding of insufficient HER2 positivity.

Reporting group values	Full analysis set		
Number of subjects	56		
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 median full range (min-max)	 62 32 to 86		
Gender categorical Units: Subjects			
Female Male	15 41		

End points

End points reporting groups

Reporting group title	Overall trial
Reporting group description: -	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Two of the enrolled patients were excluded from the full analysis set due to major violations of in- and exclusion criteria. In one case, the finding peritoneal carcinomatosis led to the retrospective exclusion of the patient from the FAS. In the other case, exclusion from the FAS was due to the retrospective finding of insufficient HER2 positivity.

Primary: Rate of pathologic complete response (pCR)

End point title	Rate of pathologic complete response (pCR)

End point description:

Histological regression grading according to Becker from tumor resectate.

End point type	Primary

End point timeframe:

Assessed from tumor resectate after four cycles of treatment

End point values	Overall trial	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	56	56		
Units: cases of complete response	12	12		

Statistical analyses

Statistical analysis title	Pathological complete response (pCR) rate

Statistical analysis description:

A doubling of the pCR rate by HerFLOT therapy as assessed by central pathology (and assumed as amounting to 10% after chemotherapy only) was considered a positive finding.
In the FAS, 12 (21.4%, 95% CI: 11.6 – 34.4) of the patients experienced a pCR. The lower border of the one-sided 90% CI (corresponding to the 10% type I error defined at the design stage) amounts to 14.4%, thus being distinctly above the pre-defined futility level of 10% pCR.

Comparison groups	Overall trial v Full analysis set
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	: confidence interval (historical compar
Point estimate	21.4
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	14.4
upper limit	30.1

Secondary: Relapse-free survival

End point title	Relapse-free survival

End point description:

Only 19 relapse events were observed during follow-up. The formally derived median RFS is 42,5 months (95% CI: 36,5 – undefined).

End point type	Secondary

End point timeframe:

Relapse-free survival was measured from the time point of surgery until disease recurrence.

End point values	Overall trial	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	56	56		
Units: Relapse events	19	19		

Attachments (see zip file)	HerFLOT_RFS_Kaplan-Meier/HerFLOT_RFS.PNG

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Number of deaths observed during the follow-up period (median 36 months).

End point values	Overall trial	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	56	56		
Units: Deaths	13	13		

Attachments (see zip file)	HerFLOT_OS_Kaplan-Meier/HerFLOT_OS.PNG

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of R0 resection

End point title	Rate of R0 resection

End point description:

End point type	Secondary

End point timeframe:

At surgery

End point values	Overall trial	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	56	56		
Units: Number of R0-resected tumors	52	52		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events reported here are treatment emergent adverse events (TEAE). AE assessment was carried out with every treatment cycle, for EoT at day 22 after last treatment, and then every 3 months until end of follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 58 (55.17%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic gastric cancer			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Polyp			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subclavian vein thrombosis			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Abdominal pain upper			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Hyperplasia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Thrombosis in device			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Bronchitis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	3 / 58 (5.17%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary fibrosis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Mental disorder due to a general medical condition				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Aspartate aminotransferase increased				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigation				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transaminases increased				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
White blood cell count decreased				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Anastomotic complication				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural complication				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural pulmonary embolism				

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seroma			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cervicobrachial syndrome			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	4 / 58 (6.90%)			
occurrences causally related to treatment / all	4 / 6			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	3 / 58 (5.17%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hiatus hernia				
subjects affected / exposed	2 / 58 (3.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	3 / 58 (5.17%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Nausea				
subjects affected / exposed	2 / 58 (3.45%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Oesophageal stenosis				

subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal haemorrhage				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth disorder				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 58 (5.17%)			
occurrences causally related to treatment / all	3 / 8			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hypersensitivity				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Urticaria				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				

Renal failure				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Device related infection				
subjects affected / exposed	2 / 58 (3.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	2 / 58 (3.45%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Intervertebral discitis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 58 (3.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Decreased appetite			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypophagia			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 58 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	15		
Hypertension			
subjects affected / exposed	11 / 58 (18.97%)		
occurrences (all)	16		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	7		
Chest pain			

subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Chills			
subjects affected / exposed	15 / 58 (25.86%)		
occurrences (all)	21		
Fatigue			
subjects affected / exposed	37 / 58 (63.79%)		
occurrences (all)	58		
Mucosal inflammation			
subjects affected / exposed	18 / 58 (31.03%)		
occurrences (all)	25		
Oedema			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	9 / 58 (15.52%)		
occurrences (all)	12		
Pain			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	24 / 58 (41.38%)		
occurrences (all)	41		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	6		
Dyspnoea			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Epistaxis			

subjects affected / exposed	15 / 58 (25.86%)		
occurrences (all)	22		
Nasal dryness			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	7		
Nasopharyngitis			
subjects affected / exposed	10 / 58 (17.24%)		
occurrences (all)	16		
Pleural effusion			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	4		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	3		
Sleep disorder			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Product issues			
Thrombosis in device			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	5		
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Blood lactate dehydrogenase increased			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	6		
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	4		
Hypokalaemia			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	5		
Neutrophil count decreased			
subjects affected / exposed	30 / 58 (51.72%)		
occurrences (all)	58		
White blood cell count decreased			
subjects affected / exposed	30 / 58 (51.72%)		
occurrences (all)	66		
Injury, poisoning and procedural complications			
Anastomotic complication			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Neurotoxicity			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	9		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	13		
Paraesthesia			
subjects affected / exposed	15 / 58 (25.86%)		
occurrences (all)	23		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	4		
Peripheral sensory neuropathy			
subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	9		
Polyneuropathy			

subjects affected / exposed	29 / 58 (50.00%)		
occurrences (all)	34		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 58 (20.69%)		
occurrences (all)	16		
Thrombocytopenia			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	9		
Abdominal pain			
subjects affected / exposed	15 / 58 (25.86%)		
occurrences (all)	22		
Abdominal pain upper			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	12 / 58 (20.69%)		
occurrences (all)	13		
Diarrhoea			
subjects affected / exposed	44 / 58 (75.86%)		
occurrences (all)	144		
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	40 / 58 (68.97%)		
occurrences (all)	92		
Post gastric surgery syndrome			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Stomatitis			

subjects affected / exposed	11 / 58 (18.97%)		
occurrences (all)	15		
Toothache			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	26 / 58 (44.83%)		
occurrences (all)	38		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	34 / 58 (58.62%)		
occurrences (all)	34		
Dry skin			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	7		
Onychoclasis			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	12 / 58 (20.69%)		
occurrences (all)	14		
Pigmentation disorder			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	5		
Pruritus			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	5		
Rash			
subjects affected / exposed	11 / 58 (18.97%)		
occurrences (all)	12		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	3		
Back pain			

subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	8		
Muscle spasms			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Infections and infestations			
Infection			
subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	12		
Oral candidiasis			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	4		
Pneumonia			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	5		
Sepsis			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	19 / 58 (32.76%)		
occurrences (all)	40		
Dysgeusia			
subjects affected / exposed	11 / 58 (18.97%)		
occurrences (all)	16		
Dyspepsia			
subjects affected / exposed	9 / 58 (15.52%)		
occurrences (all)	12		
Dysphagia			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	8		
Weight decreased			

subjects affected / exposed occurrences (all)	40 / 58 (68.97%) 40		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2012	Change of Sponsor address
16 October 2014	Implementation of updates in the Summaries of Product Characteristics (SmPCs) of trastuzumab and chemotherapy drugs regarding side effects and trastuzumab half-life. Study protocol and patient informed consent were updated accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34019698