Clinical trial results:
AN OPEN-LABEL, MULTICENTER, RANDOMIZED, PHASE 3 STUDY OF S-1 AND CISPLATIN COMPARED WITH 5-FU AND CISPLATIN IN PATIENTS WITH METASTATIC DIFFUSE GASTRIC CANCER PREVIOUSLY UNTREATED WITH CHEMOTHERAPY

Summary

EudraCT number	2009-016019-39
Trial protocol	DE BE HU GB ES PT EE IT BG LT
Global end of trial date	15 August 2014

Results information

Result version number	v1 (current)
This version publication date	02 November 2020
First version publication date	02 November 2020
Summary attachment (see zip file)	2009-016019-39 - TPU-S-1303 Final CSR Summary (2009-016019-39 - TPU-S-1303 Final CSR Synopsis _23Jan2014.pdf)

Trial information

Trial identification

Sponsor protocol code	TPU-S1303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01285557
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Taiho Oncology, Inc.
Sponsor organisation address	202 Carnegie Center, Suite 100, Princeton, United States, 08540
Public contact	Takekazu Aoyama, Taiho Oncology, Inc., 1 6097505300, aoyama@taihopui.com
Scientific contact	Takekazu Aoyama, Taiho Oncology, Inc., 1 6097505300, aoyama@taihopui.com

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	23 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2014
Global end of trial reached?	Yes
Global end of trial date	15 August 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the following endpoints for the S-1/cisplatin regimen (experimental arm) with the 5-FU/cisplatin regimen control arm) in patients with metastatic diffuse gastric cancer:

- overall survival (OS)

Protection of trial subjects:

This study was conducted and informed consent was obtained according to the ethical principles that have their origins in the Declaration of Helsinki and its amendments, and in accordance with Title 21 CFR 312.50 through 312.70, the International Conference on Harmonisation (ICH) Tripartite Guidelines for Good Clinical Practice, and local and national laws and regulations relevant to the use of investigational therapeutic agents.

Patients were monitored for safety from the time of signed informed consent form through 30 days after the last dose of study medication or until the start of new antitumor therapy, whichever was earlier. Adverse events were coded using the Medical Dictionary for Regulatory Activities Dictionary (MedDRA), Version 14.0, and were categorized by system organ class (SOC) and preferred term (PT). Treatment-related SAEs that occurred after the 30-day follow-up.

Patients were followed for survival status every 8 weeks until death or until 2 years after the last patient was randomized in the study. During follow-up, CT scans were performed every 8 weeks until the occurrence of radiologic progression or the start of a new antitumor therapy.

Background therapy: -

Evidence for comparator:

At the present time, there is no universally accepted standard regimen in the treatment of front-line metastatic gastric cancer. Fluoropyrimidine- and platinum-based chemotherapies, as a doublet or as the backbone of triplet therapy, have been standard regimens used in the treatment of metastatic gastric cancer over several decades. Despite multiple randomized studies and meta-analyses, the definitive superiority of anthracycline-based triplet therapy over standard fluoropyrimidine-platinum based regimens has not been established.

The control arm of this study employs a fluorpyrimidine-platinum regimen that is commonly used by community oncologists and has been accepted as a standard control regimen by regulatory authorities in both Europe and the United States: 5-FU 800 mg/m2/24 hours administered as a CIV on Days 1 through 5 following 80 mg/m2 cisplatin administered IV as a 1- to 3-hour infusion on Day 1. This regimen is repeated every 21 days.

Actual start date of recruitment	14 April 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	United States: 32
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Brazil: 18
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	Ukraine: 117
Country: Number of subjects enrolled	Russian Federation: 71
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Estonia: 10
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Italy: 19
Worldwide total number of subjects	361
EEA total number of subjects	110

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)	292
From 65 to 84 years	54
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

The study enrolled male and female patients ≥18 years of age with histologically confirmed by Central Pathology Review, unresectable (at the time of screening for study eligibility), metastatic diffuse gastric cancer including carcinoma of the gastro-esophageal junction who had no prior chemotherapy for gastric cancer.

Pre-assignment

Screening details:

All patients completed the following study procedures prior to a confirmation of eligibility: Signed ICF, Body Weight measurement, ECOG performance status, Infection Assessment, Histological Confirmation, Medical History, Audiogram, ECG, Chest X-ray (CXR), Tumor Measurements, Physical Exam, Vital Signs, Height, Baseline Signs & Symptoms and so on.

Pre-assignment period milestones

Number of subjects started	690[1]
Number of subjects completed	361

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen Failure: 329

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 690 patients signed the ICF and started screening and out of 690patients, 329 patients screened failed and
therefore 361 patients were randomized

Period 1

Period 1 title	Baseline Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Baseline

Arm description:

Baseline period; screening for eligibility in the study

Arm type	Baseline
Investigational medicinal product name	S-1
Investigational medicinal product code	L01BC53
Other name	Tegafur/gimeracil/oteracil
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

S-1 is an immediate release dosage form contained in hard gelatin capsules in which tegafur (FT), gimeracil (CDHP), and oteracil as monopotassium salt (Oxo) are combined at a molar ratio of 1:0.4:1. S-1 25 mg/m² was administered orally twice daily (BID) every 12 hours from Day 1 through Day 21 followed by a 7 day rest period on Days 22 to 28. This regimen was repeated every 28 days. S-1 was administered 1 hour before or 1 hour after a meal with a glass of water. Lot numbers were: 15-mg capsules, 0183, 2188, and 8G86; 20-mg capsules, 9E81, 1I91, and 13L8820.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	Cisplatinum, platamin, neoplatin, cismaplat, cis-diamminedichloridoplatinum(II) (CDDP)
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin used in the study was the commercially available product.
Cisplatin 75 mg/m2 was administered intravenously (IV) as a 1- to 3-hour infusion on Day 1 following the morning dose of S-1. This regimen was repeated every 28 days for a maximum of 8 cycles.

Investigational medicinal product name	5-FU
Investigational medicinal product code	L01BC02
Other name	Fluorouracil
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The 5-FU used in the study was the commercially available product.
5-FU 800 mg/m2/24 hours was administered intravenously (IV) by continuous infusion over 120 hours (on Days 1 through 5) followed by a 16-day rest period on Days 6 through 21. This regimen was repeated every 3 weeks.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	Cisplatinum, platamin, neoplatin, cismaplat, cis-diamminedichloridoplatinum(II) (CDDP)
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin used in the study was the commercially available product.
Cisplatin 80 mg/m2 was administered intravenously (IV) as a 1- to 3-hour infusion on Day 1 prior to the start of the 5-FU infusion on Day 1 for a maximum of 8 cycles. This regimen was repeated every 21 days.

Number of subjects in period 1	Baseline
Started	361
Signed ICF	361
Body Weight	361
ECOG Performance Status	361
Infection Assessment	361
Histological Confirmation	361
Medical History	361
Audiogram	361
ECG	361
Chest X-ray (optional)	361
Tumor Measurements	361
Physical Exam	361
Vital Signs	361
Height	361
Baseline Signs & Symptoms	361
Hematology	361
Chemistry	361

Urinalysis	361
Pregnancy Test	361
International Normalized Ratio (INR)	361
Healthcare Utilization	361
AE/SAE Assessments	361
Concomitant Medications	361
Completed	361

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	S-1/Cisplatin (experimental arm)

Arm description:

Experimental arm, evaluating the efficacy and safety of the S-1/cisplatin regimen in chemotherapy-naïve patients with metastatic diffuse gastric
cancer including carcinoma of the gastro-esophageal junction. Patients were stratified by: histologic subtype (adenocarcinoma, diffuse type or signet ring cell adenocarcinoma); extent of metastasis (1 versus more than 1 metastatic site); Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1); and Region (North America/Western Europe/Eastern Europe/Rest of World [ROW]).

Arm type	Experimental
Investigational medicinal product name	S-1
Investigational medicinal product code	L01BC53
Other name	Tegafur/gimeracil/oteracil
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

S-1 is an immediate release dosage form contained in hard gelatin capsules in which tegafur (FT), gimeracil (CDHP), and oteracil as monopotassium salt (Oxo) are combined at a molar ratio of 1:0.4:1. S-1 25 mg/m² was administered orally twice daily (BID) every 12 hours from Day 1 through Day 21 followed by a 7 day rest period on Days 22 to 28. This regimen was repeated every 28 days. S-1 was administered 1 hour before or 1 hour after a meal with a glass of water. Lot numbers were: 15-mg capsules, 0183, 2188, and 8G86; 20-mg capsules, 9E81, 1I91, and 13L8820.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	Cisplatinum, platamin, neoplatin, cismaplat, cis-diamminedichloridoplatinum(II) (CDDP)
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin used in the study was the commercially available product.
Cisplatin 75 mg/m2 was administered intravenously (IV) as a 1- to 3-hour infusion on Day 1 following the morning dose of S-1. This regimen was repeated every 28 days for a maximum of 8 cycles.

Arm title	5-FU/Cisplatin (control arm)

Arm description:

Control arm, evaluating the efficacy and safety of 5-FU/Cisplatin regimen in chemotherapy-naïve patients with metastatic diffuse gastric carcinoma including carcinoma of the gastro-esophageal junction. Patients were stratified by: histologic subtype (adenocarcinoma, diffuse type or signet ring cell adenocarcinoma); extent of metastasis (1 versus more than 1 metastatic site); Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1); and Region (North America/Western Europe/Eastern Europe/Rest of World [ROW]).

Arm type	Active comparator
Investigational medicinal product name	5-FU
Investigational medicinal product code	L01BC02
Other name	Fluorouracil
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The 5-FU used in the study was the commercially available product.
5-FU 800 mg/m2/24 hours was administered intravenously (IV) by continuous infusion over 120 hours (on Days 1 through 5) followed by a 16-day rest period on Days 6 through 21. This regimen was repeated every 3 weeks.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	Cisplatinum, platamin, neoplatin, cismaplat, cis-diamminedichloridoplatinum(II) (CDDP)
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin used in the study was the commercially available product.
Cisplatin 80 mg/m2 was administered intravenously (IV) as a 1- to 3-hour infusion on Day 1 prior to the start of the 5-FU infusion on Day 1 for a maximum of 8 cycles. This regimen was repeated every 21 days.

Number of subjects in period 2	S-1/Cisplatin (experimental arm)	5-FU/Cisplatin (control arm)
Started	239	122
Randomization	239	122
Body Weight	239	122
ECOG Performance Status	239	122
Audiogram	239	122
Chest X-ray (CXR)	239	122
Tumor Assessments	239	122
Physical Exam	239	122
Vital Signs	239	122
Hematology	239	122
Chemistry	239	122
Urinalysis	239	122
INR	239	122
Arm A (S-1) or Arm B (5-FU) treatment	238	121
Hydration	239	122

Healthcare Utilization	239	122
AE/SAE Assessments	239	122
Concomitant Medications	239	122
Completed	238	121
Not completed	1	1
Randomized but not Treated	1	1

Period 3	
Period 3 title	End of Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	S-1/Cisplatin (experimental arm)
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	5-FU/Cisplatin (control arm)
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	S-1/Cisplatin (experimental arm)	5-FU/Cisplatin (control arm)
Started	238	121
Body Weight	238	121
ECOG Performance Status	238	121
Audiogram	238	121
Chest X-Ray (CXR) (optional)	238	121
Tumor Assessments	238	121
Physical Exam	238	121
Vital Signs	238	121
Hematology	238	121
Chemistry	238	121
Urinalysis	238	121
INR	238	121
Healthcare Utilization	238	121

AE/SAE Assessments	238	121
Concomitant Medications	238	121
Survival follow-up	238	121
Completed	19	10
Not completed	219	111
Consent withdrawn by subject	14	13
Physician decision	4	2
Adverse event, non-fatal	22	10
Clinical disease progression	46	23
Lost to follow-up	2	4
Radiologic progression	127	59
Protocol deviation	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
Baseline period; screening for eligibility in the study	

Reporting group values	Baseline	Total	
Number of subjects	361	361	
Age categorical Units: Subjects			
Adults (18-64 years)	292	292	
From 65-84 years	69	69	
Age continuous Units: years			
median	55.4		
standard deviation	± 11.27	-	
Gender categorical Units: Subjects			
Female	177	177	
Male	184	184	
Race Units: Subjects			
Caucasian/White	343	343	
Black	6	6	
Asian/Oriental	4	4	
American Indian or Alaska Native	2	2	
Other	6	6	
Ethnicity Units: Subjects			
Hispanic or Latino	39	39	
Not Hispanic or Latino	321	321	
Not Collected	1	1	
Weight Units: kg			
arithmetic mean	67.6		
standard deviation	± 15.44	-	
Height Units: cm			
arithmetic mean	166.5		
standard deviation	± 9.13	-	
Body Surface Area (BSA) Units: m2			
arithmetic mean	1.749		
standard deviation	± 0.2062	-	

Subject analysis sets	
Subject analysis set title	Intention to treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT population - Total patients who were randomized	
Subject analysis set title	Intention to treat (ITT) - S-1/Cisplatin
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention to treat (ITT) population in the S-1/Cisplatin experimental group	
Subject analysis set title	Intention to treat (ITT) - 5-FU/Cisplatin
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention to treat (ITT) population in the 5-FU/Cisplatin control group	

Reporting group values	Intention to treat (ITT)	Intention to treat (ITT) - S-1/Cisplatin	Intention to treat (ITT) - 5-FU/Cisplatin
Number of subjects	361	239	122
Age categorical Units: Subjects			
Adults (18-64 years)	292	199	93
From 65-84 years	69	40	29
Age continuous Units: years			
median	55.4	55.1	55.8
standard deviation	± 11.27	± 11.01	± 11.80
Gender categorical Units: Subjects			
Female	177	115	62
Male	184	124	60
Race Units: Subjects			
Caucasian/White	343	226	117
Black	6	4	2
Asian/Oriental	4	4	0
American Indian or Alaska Native	2	2	0
Other	6	3	3
Ethnicity Units: Subjects			
Hispanic or Latino	39	26	13
Not Hispanic or Latino	321	213	108
Not Collected	1	0	1
Weight Units: kg			
arithmetic mean	67.6	67.5	67.7
standard deviation	± 15.44	± 16.16	± 13.98
Height Units: cm			
arithmetic mean	166.5	166.4	166.8
standard deviation	± 9.13	± 9.53	± 8.31
Body Surface Area (BSA) Units: m2			

arithmetic mean	1.749	1.746	1.754
standard deviation	± 0.2062	± 0.2147	± 0.1889

End points

End points reporting groups

Reporting group title	Baseline
Reporting group description:	
Baseline period; screening for eligibility in the study	
Reporting group title	S-1/Cisplatin (experimental arm)
Reporting group description:	
Experimental arm, evaluating the efficacy and safety of the S-1/cisplatin regimen in chemotherapy-naïve patients with metastatic diffuse gastric cancer including carcinoma of the gastro-esophageal junction. Patients were stratified by: histologic subtype (adenocarcinoma, diffuse type or signet ring cell adenocarcinoma); extent of metastasis (1 versus more than 1 metastatic site); Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1); and Region (North America/Western Europe/Eastern Europe/Rest of World [ROW]).	
Reporting group title	5-FU/Cisplatin (control arm)
Reporting group description:	
Control arm, evaluating the efficacy and safety of 5-FU/Cisplatin regimen in chemotherapy-naïve patients with metastatic diffuse gastric carcinoma including carcinoma of the gastro-esophageal junction. Patients were stratified by: histologic subtype (adenocarcinoma, diffuse type or signet ring cell adenocarcinoma); extent of metastasis (1 versus more than 1 metastatic site); Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1); and Region (North America/Western Europe/Eastern Europe/Rest of World [ROW]).	
Reporting group title	S-1/Cisplatin (experimental arm)
Reporting group description: -	
Reporting group title	5-FU/Cisplatin (control arm)
Reporting group description: -	
Subject analysis set title	Intention to treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
ITT population - Total patients who were randomized	
Subject analysis set title	Intention to treat (ITT) - S-1/Cisplatin
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to treat (ITT) population in the S-1/Cisplatin experimental group	
Subject analysis set title	Intention to treat (ITT) - 5-FU/Cisplatin
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to treat (ITT) population in the 5-FU/Cisplatin control group	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Overall Survival (OS) was the primary endpoint of this study and was defined as the time from the day of randomization to the date of death for the Intent-to-treat (ITT) population. Patients who did not die as of the OS cut-off date were censored at the date last known to be alive. The difference in OS between the 2 treatment groups was assessed using the unstratified log-rank test (Score statistic from PHREG and ties=Breslow). Survival for each group was summarized using Kaplan Meier curves and was further characterized in terms of the median and survival probability at 3, 6, 9 and 12 months, along with the corresponding 2-sided 95% confidence intervals for the estimates. Confidence intervals (CIs) for median survival were based upon the methods of Brookmeyer and Crowley. The influence of stratification factors and other baseline characteristics was assessed using the stratified log-rank test and Cox's regression approach.	
End point type	Primary
End point timeframe:	
The time from randomization to the date of death for the Intent-to-treat (ITT) population.	

End point values	S-1/Cisplatin (experimental arm)	5-FU/Cisplatin (control arm)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	122		
Units: months				
median (confidence interval 95%)	7.5 (6.7 to 9.3)	6.6 (5.7 to 8.1)		

Statistical analyses

Statistical analysis title	Overall survival (OS)

Statistical analysis description:

The difference in OS between the 2 treatment groups was assessed using the unstratified log-rank test (Score statistic from PHREG and ties=Breslow). Survival for each group was summarized using Kaplan Meier curves and was further characterized in terms of the median and survival probability at 3, 6, 9 and 12 months, along with the corresponding 2-sided 95% confidence intervals for the estimates.
Confidence intervals (CIs) for median survival
were based upon the methods of Brookmeyer and Crowley

Comparison groups	S-1/Cisplatin (experimental arm) v 5-FU/Cisplatin (control arm)
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9312
Method	t-test, 2-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.28
Variability estimate	Standard deviation

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival was defined as the time from date of randomization until date of radiological disease progression or death due to any cause. Patients who were alive with no disease progression were censored at the date of the last tumor assessment. Patients who received new anticancer therapy before disease progression were censored at the date of the last evaluable tumor assessment before new anticancer therapy was initiated.

End point type	Secondary

End point timeframe:

Progression-free survival was defined as the time from date of randomization until date of radiological disease progression or death due to any cause.

End point values	S-1/Cisplatin (experimental arm)	5-FU/Cisplatin (control arm)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	122		
Units: months				
median (confidence interval 95%)	4.4 (3.8 to 5.6)	3.9 (3.6 to 5.2)		

Statistical analyses

Statistical analysis title	Progression-Free Survival (months)
Statistical analysis description:	
Progression-Free Survival (PFS) were analyzed using the same methods as for the primary endpoint - Overall Survival (OS).	
Comparison groups	S-1/Cisplatin (experimental arm) v 5-FU/Cisplatin (control arm)
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3039
Method	t-test, 2-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.14
Variability estimate	Standard deviation

Secondary: Time to treatment failure (TTF)

End point title	Time to treatment failure (TTF)
End point description:	
Time to treatment failure was defined as the time from date of randomization until date of disease progression (clinical or radiologic), or permanent discontinuation of study treatment (S-1 or 5-FU), or death due to any cause. Patients who were still on study treatment at the time of the analysis were censored at the last date the patient was known to be on treatment.	
End point type	Secondary
End point timeframe:	
Time to treatment failure was defined as the time from date of randomization until date of disease progression (clinical or radiologic), or permanent discontinuation of study treatment (S-1 or 5-FU), or death due to any cause.	

End point values	S-1/Cisplatin (experimental arm)	5-FU/Cisplatin (control arm)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	122		
Units: months				
median (confidence interval 95%)	4.2 (3.8 to 4.9)	3.8 (3.4 to 4.3)		

Statistical analyses

Statistical analysis title	Time to treatment failure (TTF)

Statistical analysis description:

Time to treatment failure (TTF) was analyzed using the same methods as for the primary endpoint Overall Survival (OS).

Comparison groups	S-1/Cisplatin (experimental arm) v 5-FU/Cisplatin (control arm)
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1683
Method	t-test, 2-sided
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.08
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patients were monitored for safety from the time of signed informed consent form through 30 days after the last dose of study medication or until the start of new antitumor therapy, whichever was earlier.

Adverse event reporting additional description:

Adverse events were coded using the Medical Dictionary for Regulatory Activities Dictionary (MedDRA), Version 14.0, and were categorized by system organ class (SOC) and preferred term (PT).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	S-1/Cisplatin (As Treated Population)

Reporting group description:

Adverse Events occurring in subjects within the S-1/Cisplatin group (As Treated Population)

Reporting group title	5-FU/Cisplatin (As Treated Population)

Reporting group description:

Adverse Events occurring in subjects within the 5-FU/Cisplatin group (As Treated Population)

Serious adverse events	S-1/Cisplatin (As Treated Population)	5-FU/Cisplatin (As Treated Population)	
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 230 (27.39%)	31 / 118 (26.27%)	
number of deaths (all causes)	169	89	
number of deaths resulting from adverse events	17	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Paraneoplastic Syndrome			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 230 (1.30%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (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	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Disease progression			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Device Dislocation			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
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	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infusion Site Extravasation			

subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal Inflammation			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural Effusion			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Artery Thrombosis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (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	2 / 230 (0.87%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional State			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Blood Creatinine Increased			
subjects affected / exposed	3 / 230 (1.30%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil Count Decreased			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Fracture			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity To Various Agents			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytotoxic Cardiomyopathy			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Haemorrhage			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Convulsion			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrapyramidal Disorder			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Parkinson's Disease			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 230 (4.78%)	5 / 118 (4.24%)	
occurrences causally related to treatment / all	0 / 12	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	0 / 230 (0.00%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal Distension			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	3 / 230 (1.30%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain Upper			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	4 / 230 (1.74%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	3 / 230 (1.30%)	4 / 118 (3.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric Perforation			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Gastric Stenosis			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal Obstruction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (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	1 / 230 (0.43%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	3 / 230 (1.30%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large Intestinal Obstruction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Melaena			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	4 / 230 (1.74%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction Gastric			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	5 / 230 (2.17%)	4 / 118 (3.39%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary Colic			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis Acute			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice Cholestatic			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis Infectious			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Failure Acute			
subjects affected / exposed	5 / 230 (2.17%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric Obstruction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Obstruction			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal Infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary Tract Infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Sepsis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 230 (1.30%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic Shock			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (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			

Decreased Appetite			
subjects affected / exposed	3 / 230 (1.30%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	6 / 230 (2.61%)	4 / 118 (3.39%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 230 (0.00%)	4 / 118 (3.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	S-1/Cisplatin (As Treated Population)	5-FU/Cisplatin (As Treated Population)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	214 / 230 (93.04%)	111 / 118 (94.07%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibroma			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	

Malignant Ascites			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Papilloma			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Paraneoplastic Syndrome			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Aortic Aneurysm			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Capillary Fragility			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Deep Vein Thrombosis			
subjects affected / exposed	11 / 230 (4.78%)	3 / 118 (2.54%)	
occurrences (all)	12	3	
Dizziness			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Embolism			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Flushing			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Hot Flush			
subjects affected / exposed	2 / 230 (0.87%)	2 / 118 (1.69%)	
occurrences (all)	2	2	
Hyperaemia			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	3 / 230 (1.30%)	2 / 118 (1.69%)	
occurrences (all)	4	3	
Hypertensive Crisis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	2 / 230 (0.87%)	4 / 118 (3.39%)	
occurrences (all)	3	4	
Hypovolaemic Shock			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Lymphoedema			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Orthostatic Hypotension			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Pallor			
subjects affected / exposed	4 / 230 (1.74%)	0 / 118 (0.00%)	
occurrences (all)	4	0	
Pelvic Venous Thrombosis			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Peripheral Coldness			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Petechiae			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Phlebitis			
subjects affected / exposed	2 / 230 (0.87%)	3 / 118 (2.54%)	
occurrences (all)	2	4	
Pulmonary Embolism			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Subclavian Vein Thrombosis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Thrombosis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Venous Valve Ruptured			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Administration Site Pain			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Application Site Pain			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Application Site Reaction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Asthenia			
subjects affected / exposed	56 / 230 (24.35%)	36 / 118 (30.51%)	
occurrences (all)	81	61	
Catheter Site Haemorrhage			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Catheter Site Pain			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Catheter Site Phlebitis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Catheter Site Pruritus			

subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Catheter Site Rash			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Chest Discomfort			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Chest Pain			
subjects affected / exposed	3 / 230 (1.30%)	1 / 118 (0.85%)	
occurrences (all)	4	1	
Chills			
subjects affected / exposed	3 / 230 (1.30%)	0 / 118 (0.00%)	
occurrences (all)	3	0	
Death			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Device Dislocation			
subjects affected / exposed	0 / 230 (0.00%)	2 / 118 (1.69%)	
occurrences (all)	0	2	
Device Occlusion			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Disease Progression			
subjects affected / exposed	3 / 230 (1.30%)	1 / 118 (0.85%)	
occurrences (all)	3	1	
Early Satiety			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Facial Pain			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	59 / 230 (25.65%)	28 / 118 (23.73%)	
occurrences (all)	104	51	
Feeling Cold			

subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
General Physical Health Deterioration			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Generalised Oedema			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Hyperthermia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Implant Site Discharge			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Infusion Site Extravasation			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Infusion Site Swelling			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Injection Site Erythema			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Injection Site Swelling			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Local Swelling			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Localised Oedema			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Malaise			
subjects affected / exposed	5 / 230 (2.17%)	1 / 118 (0.85%)	
occurrences (all)	6	1	
Mucosal Dryness			

subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)		
occurrences (all)	2	0		
Mucosal Inflammation				
subjects affected / exposed	20 / 230 (8.70%)	20 / 118 (16.95%)		
occurrences (all)	24	37		
Nodule				
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)		
occurrences (all)	0	1		
Non-Cardiac Chest Pain				
subjects affected / exposed	5 / 230 (2.17%)	0 / 118 (0.00%)		
occurrences (all)	6	0		
Oedema				
subjects affected / exposed	1 / 230 (0.43%)	2 / 118 (1.69%)		
occurrences (all)	1	2		
Oedema Peripheral				
subjects affected / exposed	17 / 230 (7.39%)	7 / 118 (5.93%)		
occurrences (all)	20	9		
Pain				
subjects affected / exposed	3 / 230 (1.30%)	1 / 118 (0.85%)		
occurrences (all)	3	1		
Pyrexia				
subjects affected / exposed	19 / 230 (8.26%)	7 / 118 (5.93%)		
occurrences (all)	28	9		
Suprapubic Pain				
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)		
occurrences (all)	1	1		
Systemic Inflammatory Response Syndrome				
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)		
occurrences (all)	1	0		
Temperature Intolerance				
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)		
occurrences (all)	1	1		
Xerosis				
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)		
occurrences (all)	1	0		

Biliary Colic			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Cholangitis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Cholecystitis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Contrast Media Allergy			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Drug Hypersensitivity			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Hypersensitivity			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Seasonal Allergy			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Pelvic Pain			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Retracted Nipple			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Vulvovaginal Pain			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Acute Respiratory Failure				
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)		
occurrences (all)	1	0		
Atelectasis				
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)		
occurrences (all)	1	0		
Bronchospasm				
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)		
occurrences (all)	0	1		
Chronic Obstructive Pulmonary Disease				
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)		
occurrences (all)	0	1		
Cough				
subjects affected / exposed	15 / 230 (6.52%)	5 / 118 (4.24%)		
occurrences (all)	19	5		
Dysphonia				
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)		
occurrences (all)	1	0		
Dyspnoea				
subjects affected / exposed	19 / 230 (8.26%)	8 / 118 (6.78%)		
occurrences (all)	26	13		
Epistaxis				
subjects affected / exposed	4 / 230 (1.74%)	1 / 118 (0.85%)		
occurrences (all)	5	1		
Hiccups				
subjects affected / exposed	9 / 230 (3.91%)	0 / 118 (0.00%)		
occurrences (all)	12	0		
Hydrothorax				
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)		
occurrences (all)	1	0		
Hypoventilation				
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)		
occurrences (all)	1	0		
Hypoxia				

subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Nasal Discomfort			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Nasal Dryness			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Nasal Inflammation			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal Pain			
subjects affected / exposed	9 / 230 (3.91%)	2 / 118 (1.69%)	
occurrences (all)	11	2	
Pleural Effusion			
subjects affected / exposed	4 / 230 (1.74%)	2 / 118 (1.69%)	
occurrences (all)	4	2	
Pleurisy			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Pleuritic Pain			
subjects affected / exposed	3 / 230 (1.30%)	0 / 118 (0.00%)	
occurrences (all)	4	0	
Pneumonitis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Productive Cough			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Pulmonary Artery Thrombosis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Pulmonary Embolism			
subjects affected / exposed	7 / 230 (3.04%)	3 / 118 (2.54%)	
occurrences (all)	8	3	
Pulmonary Infarction			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Respiratory Distress			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Respiratory Tract Congestion			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Rhinitis Allergic			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Rhinorrhoea			
subjects affected / exposed	3 / 230 (1.30%)	1 / 118 (0.85%)	
occurrences (all)	3	1	
Sinus Congestion			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	3	0	
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	4 / 230 (1.74%)	1 / 118 (0.85%)	
occurrences (all)	7	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 230 (2.61%)	2 / 118 (1.69%)	
occurrences (all)	7	8	
Bradyphrenia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Confusional State			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Depression			
subjects affected / exposed	6 / 230 (2.61%)	0 / 118 (0.00%)	
occurrences (all)	6	0	
Disorientation			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	13 / 230 (5.65%)	5 / 118 (4.24%)	
occurrences (all)	14	5	
Mental Status Changes			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Panic Attack			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Stress			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	9 / 230 (3.91%)	4 / 118 (3.39%)	
occurrences (all)	11	4	
Aspartate Aminotransferase Increased			
subjects affected / exposed	12 / 230 (5.22%)	4 / 118 (3.39%)	
occurrences (all)	13	4	
Bilirubin Conjugated Increased			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	9 / 230 (3.91%)	1 / 118 (0.85%)	
occurrences (all)	10	1	
Blood Amylase Increased			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Blood Bilirubin Increased			

subjects affected / exposed	13 / 230 (5.65%)	1 / 118 (0.85%)		
occurrences (all)	17	1		
Blood Chloride Decreased				
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)		
occurrences (all)	1	0		
Blood Creatinine Increased				
subjects affected / exposed	23 / 230 (10.00%)	9 / 118 (7.63%)		
occurrences (all)	29	12		
Blood Lactate Dehydrogenase Increased				
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)		
occurrences (all)	1	0		
Blood Potassium Increased				
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)		
occurrences (all)	2	1		
Blood Pressure Increased				
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)		
occurrences (all)	2	0		
Blood Urea Increased				
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)		
occurrences (all)	2	0		
Body Temperature Increased				
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)		
occurrences (all)	1	0		
Breath Sounds Abnormal				
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)		
occurrences (all)	1	0		
Creatinine Renal Clearance Decreased				
subjects affected / exposed	9 / 230 (3.91%)	8 / 118 (6.78%)		
occurrences (all)	9	10		
Eastern Cooperative Oncology Group Performance Status Worsened				
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)		
occurrences (all)	0	1		
Gamma-Glutamyltransferase Increased				

subjects affected / exposed	3 / 230 (1.30%)	2 / 118 (1.69%)	
occurrences (all)	3	2	
Haemoglobin Decreased			
subjects affected / exposed	1 / 230 (0.43%)	2 / 118 (1.69%)	
occurrences (all)	1	2	
Hepatic Enzyme Increased			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Lipase Increased			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Liver Function Test Abnormal			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Lymph Node Palpable			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Lymphocyte Count Decreased			
subjects affected / exposed	4 / 230 (1.74%)	2 / 118 (1.69%)	
occurrences (all)	5	4	
Neutrophil Count Decreased			
subjects affected / exposed	4 / 230 (1.74%)	3 / 118 (2.54%)	
occurrences (all)	13	6	
Platelet Count Decreased			
subjects affected / exposed	4 / 230 (1.74%)	2 / 118 (1.69%)	
occurrences (all)	7	7	
Transaminases Increased			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Tumour Marker Increased			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Weight Decreased			
subjects affected / exposed	40 / 230 (17.39%)	18 / 118 (15.25%)	
occurrences (all)	42	18	
Weight Increased			

subjects affected / exposed	3 / 230 (1.30%)	1 / 118 (0.85%)	
occurrences (all)	3	1	
White Blood Cell Count Decreased			
subjects affected / exposed	9 / 230 (3.91%)	3 / 118 (2.54%)	
occurrences (all)	21	5	
White Blood Cells Semen Positive			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 230 (1.30%)	1 / 118 (0.85%)	
occurrences (all)	3	1	
Expired Drug Administered			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Fall			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Incision Site Erythema			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Incision Site Pain			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Laceration			
subjects affected / exposed	0 / 230 (0.00%)	2 / 118 (1.69%)	
occurrences (all)	0	2	
Overdose			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Pneumonitis Chemical			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Procedural Pain			

subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Procedural Site Reaction			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Seroma			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Spinal Fracture			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Thermal Burn			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Toxicity To Various Agents			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Acute Myocardial Infarction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Angina Pectoris			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Bradycardia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Cardiac Failure			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Cytotoxic Cardiomyopathy			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	

Intracardiac Thrombus			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Sinus Bradycardia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	2 / 230 (0.87%)	2 / 118 (1.69%)	
occurrences (all)	2	2	
Nervous system disorders			
Acoustic Neuritis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Amnesia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Aphasia			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Balance Disorder			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Cerebral Haemorrhage			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Cerebral Infarction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Cervical Root Pain			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Convulsion			

subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	16 / 230 (6.96%)	6 / 118 (5.08%)	
occurrences (all)	33	9	
Dysaesthesia			
subjects affected / exposed	3 / 230 (1.30%)	0 / 118 (0.00%)	
occurrences (all)	4	0	
Dysgeusia			
subjects affected / exposed	11 / 230 (4.78%)	5 / 118 (4.24%)	
occurrences (all)	12	7	
Dyskinesia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Extrapyramidal Disorder			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	18 / 230 (7.83%)	7 / 118 (5.93%)	
occurrences (all)	32	7	
Hemiplegia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Hypersomnia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Ischaemic Stroke			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Lethargy			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Loss Of Consciousness			

subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Neuralgia			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Neuropathy Peripheral			
subjects affected / exposed	23 / 230 (10.00%)	14 / 118 (11.86%)	
occurrences (all)	28	17	
Neurotoxicity			
subjects affected / exposed	4 / 230 (1.74%)	1 / 118 (0.85%)	
occurrences (all)	8	2	
Paraesthesia			
subjects affected / exposed	2 / 230 (0.87%)	2 / 118 (1.69%)	
occurrences (all)	2	2	
Paraparesis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Parkinson's Disease			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Peripheral Motor Neuropathy			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Peripheral Sensory Neuropathy			
subjects affected / exposed	6 / 230 (2.61%)	1 / 118 (0.85%)	
occurrences (all)	6	1	
Somnolence			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Syncope			
subjects affected / exposed	5 / 230 (2.17%)	1 / 118 (0.85%)	
occurrences (all)	6	1	
Tremor			
subjects affected / exposed	3 / 230 (1.30%)	1 / 118 (0.85%)	
occurrences (all)	3	1	
Viith Nerve Paralysis			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Agitation			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	173 / 230 (75.22%)	91 / 118 (77.12%)	
occurrences (all)	173	91	
Aplastic Anaemia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Coagulopathy			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Febrile Neutropenia			
subjects affected / exposed	2 / 230 (0.87%)	3 / 118 (2.54%)	
occurrences (all)	2	3	
Granulocytopenia			
subjects affected / exposed	13 / 230 (5.65%)	5 / 118 (4.24%)	
occurrences (all)	59	8	
Iron Deficiency Anaemia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Leukocytosis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Leukopenia			
subjects affected / exposed	31 / 230 (13.48%)	12 / 118 (10.17%)	
occurrences (all)	80	23	
Lymphadenopathy			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Neutropenia			
subjects affected / exposed	69 / 230 (30.00%)	43 / 118 (36.44%)	
occurrences (all)	163	93	

Pancytopenia			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Thrombocytopenia			
subjects affected / exposed	38 / 230 (16.52%)	11 / 118 (9.32%)	
occurrences (all)	75	13	
Thrombocytosis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Cerumen Impaction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Ear Discomfort			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Ear Pain			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Hypoacusis			
subjects affected / exposed	6 / 230 (2.61%)	3 / 118 (2.54%)	
occurrences (all)	6	3	
Neurosensory Hypoacusis			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Tinnitus			
subjects affected / exposed	19 / 230 (8.26%)	11 / 118 (9.32%)	
occurrences (all)	27	22	
Vertigo			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Vertigo Positional			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Eye disorders			

Blepharospasm			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Blindness Transient			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Dry Eye			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Eye Irritation			
subjects affected / exposed	3 / 230 (1.30%)	0 / 118 (0.00%)	
occurrences (all)	3	0	
Eye Pain			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Eye Pruritus			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	2	
Eyelid Oedema			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Eyes Sunken			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Lacrimation Increased			
subjects affected / exposed	6 / 230 (2.61%)	0 / 118 (0.00%)	
occurrences (all)	8	0	
Ocular Hyperaemia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Ocular Icterus			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	

Photophobia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Photopsia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Retinal Dystrophy			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Vision Blurred			
subjects affected / exposed	4 / 230 (1.74%)	1 / 118 (0.85%)	
occurrences (all)	5	3	
Visual Acuity Reduced			
subjects affected / exposed	3 / 230 (1.30%)	1 / 118 (0.85%)	
occurrences (all)	3	1	
Visual Impairment			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	3 / 230 (1.30%)	1 / 118 (0.85%)	
occurrences (all)	3	1	
Abdominal Distension			
subjects affected / exposed	19 / 230 (8.26%)	5 / 118 (4.24%)	
occurrences (all)	34	11	
Abdominal Mass			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Abdominal Pain			
subjects affected / exposed	44 / 230 (19.13%)	12 / 118 (10.17%)	
occurrences (all)	65	14	
Abdominal Pain Lower			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Abdominal Pain Upper			

subjects affected / exposed	17 / 230 (7.39%)	11 / 118 (9.32%)	
occurrences (all)	22	11	
Abdominal Tenderness			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Abdominal Wall Mass			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Anal Fissure			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Anal Haemorrhage			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Anal Pruritus			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Anorectal Discomfort			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Ascites			
subjects affected / exposed	13 / 230 (5.65%)	9 / 118 (7.63%)	
occurrences (all)	17	9	
Constipation			
subjects affected / exposed	39 / 230 (16.96%)	17 / 118 (14.41%)	
occurrences (all)	52	32	
Dental Caries			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	43 / 230 (18.70%)	23 / 118 (19.49%)	
occurrences (all)	76	47	
Dry Mouth			
subjects affected / exposed	3 / 230 (1.30%)	0 / 118 (0.00%)	
occurrences (all)	3	0	
Duodenal Ulcer Haemorrhage			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	8 / 230 (3.48%)	6 / 118 (5.08%)	
occurrences (all)	8	7	
Dysphagia			
subjects affected / exposed	10 / 230 (4.35%)	9 / 118 (7.63%)	
occurrences (all)	12	14	
Epigastric Discomfort			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Eructation			
subjects affected / exposed	0 / 230 (0.00%)	3 / 118 (2.54%)	
occurrences (all)	0	3	
Faeces Discoloured			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	3 / 230 (1.30%)	1 / 118 (0.85%)	
occurrences (all)	3	1	
Gastric Haemorrhage			
subjects affected / exposed	3 / 230 (1.30%)	4 / 118 (3.39%)	
occurrences (all)	3	5	
Gastric Perforation			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Gastric Stenosis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	3 / 230 (1.30%)	1 / 118 (0.85%)	
occurrences (all)	3	1	
Gastrointestinal Obstruction			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal Sounds Abnormal			
subjects affected / exposed	3 / 230 (1.30%)	0 / 118 (0.00%)	
occurrences (all)	3	0	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	2 / 230 (0.87%)	2 / 118 (1.69%)	
occurrences (all)	2	2	
Haematemesis			
subjects affected / exposed	2 / 230 (0.87%)	2 / 118 (1.69%)	
occurrences (all)	4	2	
Haemorrhagic Ascites			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Haemorrhoids			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Hiatus Hernia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Intestinal Obstruction			
subjects affected / exposed	3 / 230 (1.30%)	2 / 118 (1.69%)	
occurrences (all)	5	3	
Large Intestinal Obstruction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Lip Dry			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Melaena			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	4	0	
Nausea			
subjects affected / exposed	125 / 230 (54.35%)	62 / 118 (52.54%)	
occurrences (all)	277	132	
Obstruction Gastric			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Odynophagia			
subjects affected / exposed	1 / 230 (0.43%)	3 / 118 (2.54%)	
occurrences (all)	1	3	
Oesophageal Polyp			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Oesophagitis			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Oral Mucosal Eruption			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Pancreatitis Acute			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Paraesthesia Oral			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Periodontal Disease			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Proctalgia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Rectal Haemorrhage			
subjects affected / exposed	0 / 230 (0.00%)	3 / 118 (2.54%)	
occurrences (all)	0	3	
Reflux Gastritis			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Regurgitation			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Retching			

subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Salivary Hypersecretion			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Sensitivity Of Teeth			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	4 / 230 (1.74%)	18 / 118 (15.25%)	
occurrences (all)	4	36	
Tongue Discolouration			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Tooth Impacted			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	83 / 230 (36.09%)	35 / 118 (29.66%)	
occurrences (all)	147	63	
Hepatobiliary disorders			
Biliary Dilatation			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Cholecystitis Acute			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Hepatomegaly			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	

Hepatotoxicity			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	2	
Hyperbilirubinaemia			
subjects affected / exposed	7 / 230 (3.04%)	3 / 118 (2.54%)	
occurrences (all)	10	3	
Jaundice			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Jaundice Cholestatic			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Portal Vein Phlebitis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 230 (3.04%)	10 / 118 (8.47%)	
occurrences (all)	7	10	
Blister			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	2	
Cold Sweat			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Dermatitis Acneiform			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Dermatitis Allergic			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Dry Skin			
subjects affected / exposed	5 / 230 (2.17%)	4 / 118 (3.39%)	
occurrences (all)	7	4	
Erythema			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Ingrowing Nail			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Nail Discolouration			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Nail Disorder			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Night Sweats			
subjects affected / exposed	2 / 230 (0.87%)	2 / 118 (1.69%)	
occurrences (all)	4	2	
Onychalgia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Onychoclasis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Petechiae			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 230 (0.43%)	2 / 118 (1.69%)	
occurrences (all)	1	2	
Rash			
subjects affected / exposed	13 / 230 (5.65%)	6 / 118 (5.08%)	
occurrences (all)	16	8	
Rash Generalised			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Rash Maculo-Papular			

subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Rash Papular			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Skin Atrophy			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Skin Discolouration			
subjects affected / exposed	5 / 230 (2.17%)	0 / 118 (0.00%)	
occurrences (all)	6	0	
Skin Disorder			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Skin Hyperpigmentation			
subjects affected / exposed	4 / 230 (1.74%)	3 / 118 (2.54%)	
occurrences (all)	4	3	
Skin Lesion			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Skin Mass			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Skin Tightness			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Skin Toxicity			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Skin Ulcer			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Vascular Skin Disorder			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal Pruritus			

subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Yellow Skin			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Bladder Discomfort			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Chromaturia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Dysuria			
subjects affected / exposed	4 / 230 (1.74%)	1 / 118 (0.85%)	
occurrences (all)	4	1	
Haematuria			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Hydronephrosis			
subjects affected / exposed	3 / 230 (1.30%)	0 / 118 (0.00%)	
occurrences (all)	3	0	
Pollakiuria			
subjects affected / exposed	1 / 230 (0.43%)	2 / 118 (1.69%)	
occurrences (all)	1	2	
Renal Colic			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Renal Failure			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Renal Failure Acute			
subjects affected / exposed	5 / 230 (2.17%)	1 / 118 (0.85%)	
occurrences (all)	6	1	
Renal Failure Chronic			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	

Renal Impairment			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Renal Vein Thrombosis			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Ureteric Obstruction			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Urinary Incontinence			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Urinary Retention			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Urinary Tract Obstruction			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Urine Flow Decreased			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Scrotal Oedema			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Vaginal Discharge			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal Burning Sensation			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal Discomfort			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal Dryness			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 230 (3.04%)	0 / 118 (0.00%)	
occurrences (all)	8	0	
Back Pain			
subjects affected / exposed	16 / 230 (6.96%)	5 / 118 (4.24%)	
occurrences (all)	18	7	
Bone Pain			
subjects affected / exposed	4 / 230 (1.74%)	4 / 118 (3.39%)	
occurrences (all)	4	4	
Flank Pain			
subjects affected / exposed	3 / 230 (1.30%)	0 / 118 (0.00%)	
occurrences (all)	3	0	
Groin Pain			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Intervertebral Disc Disorder			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Joint Range Of Motion Decreased			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Lumbar Vertebral Fracture			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Muscle Spasms			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Muscle Tightness			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Muscular Weakness			

subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Musculoskeletal Chest Pain			
subjects affected / exposed	5 / 230 (2.17%)	0 / 118 (0.00%)	
occurrences (all)	5	0	
Musculoskeletal Pain			
subjects affected / exposed	3 / 230 (1.30%)	2 / 118 (1.69%)	
occurrences (all)	3	2	
Myalgia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Neck Pain			
subjects affected / exposed	5 / 230 (2.17%)	0 / 118 (0.00%)	
occurrences (all)	5	0	
Osteoarthritis			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Pain In Extremity			
subjects affected / exposed	11 / 230 (4.78%)	4 / 118 (3.39%)	
occurrences (all)	16	4	
Pain In Jaw			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Pelvic Floor Muscle Weakness			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Spinal Deformity			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Spinal Osteoarthritis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Abdominal Infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	

Biliary Tract Infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	2	
Bronchopneumonia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Candidiasis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Device Related Infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Enteritis Infectious			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Enterocolitis Infectious			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Erysipelas			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Fungal Skin Infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Herpes Zoster			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	

Hordeolum			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Impetigo			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Influenza			
subjects affected / exposed	4 / 230 (1.74%)	2 / 118 (1.69%)	
occurrences (all)	6	2	
Lobar Pneumonia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Localised Infection			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Lung Infection			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Nail Infection			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Neutropenic Sepsis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Opportunistic Infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	2	0	

Oral Candidiasis			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Oropharyngeal Candidiasis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Otitis Externa			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	5 / 230 (2.17%)	0 / 118 (0.00%)	
occurrences (all)	6	0	
Postoperative Wound Infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Pyelonephritis Acute			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Respiratory Tract Infection Viral			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Sepsis			
subjects affected / exposed	2 / 230 (0.87%)	1 / 118 (0.85%)	
occurrences (all)	2	1	
Septic Shock			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Severe Acute Respiratory Syndrome			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	

Tonsillitis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Tooth Infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 230 (1.74%)	0 / 118 (0.00%)	
occurrences (all)	4	0	
Urinary Tract Infection			
subjects affected / exposed	7 / 230 (3.04%)	2 / 118 (1.69%)	
occurrences (all)	9	4	
Viral Infection			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 230 (1.74%)	2 / 118 (1.69%)	
occurrences (all)	4	2	
Vascular Pseudoaneurysm			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Abnormal Loss Of Weight			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Alkalosis Hypochloraemic			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Cachexia			
subjects affected / exposed	1 / 230 (0.43%)	1 / 118 (0.85%)	
occurrences (all)	1	1	
Decreased Appetite			
subjects affected / exposed	96 / 230 (41.74%)	41 / 118 (34.75%)	
occurrences (all)	187	70	
Dehydration			

subjects affected / exposed	10 / 230 (4.35%)	5 / 118 (4.24%)	
occurrences (all)	13	8	
Diabetes Mellitus			
subjects affected / exposed	0 / 230 (0.00%)	1 / 118 (0.85%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	5 / 230 (2.17%)	0 / 118 (0.00%)	
occurrences (all)	5	0	
Hyperkalaemia			
subjects affected / exposed	2 / 230 (0.87%)	4 / 118 (3.39%)	
occurrences (all)	3	6	
Hypermagnesaemia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Hyperphosphataemia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminaemia			
subjects affected / exposed	6 / 230 (2.61%)	5 / 118 (4.24%)	
occurrences (all)	7	9	
Hypocalcaemia			
subjects affected / exposed	6 / 230 (2.61%)	2 / 118 (1.69%)	
occurrences (all)	8	2	
Hypoglycaemia			
subjects affected / exposed	2 / 230 (0.87%)	0 / 118 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	6 / 230 (2.61%)	10 / 118 (8.47%)	
occurrences (all)	6	19	
Hypomagnesaemia			
subjects affected / exposed	24 / 230 (10.43%)	9 / 118 (7.63%)	
occurrences (all)	31	11	
Hyponatraemia			

subjects affected / exposed	5 / 230 (2.17%)	8 / 118 (6.78%)	
occurrences (all)	7	14	
Hypophosphataemia			
subjects affected / exposed	2 / 230 (0.87%)	2 / 118 (1.69%)	
occurrences (all)	2	2	
Podagra			
subjects affected / exposed	1 / 230 (0.43%)	0 / 118 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2010	- Clarified the indication in the Protocol Synopsis. - Revised Inclusion Criterion #2 revised to indicate that histologic type will be confirmed by Central Pathology Review, and that patients may only be randomized after central pathology review has confirmed histologic type. - Increased the baseline period during which histological confirmation of metastatic diffuse gastric cancer could be obtained from the central pathology laboratory from Day -28 through Day -4 to Day -28 through Day 1 prior to randomization. - Clarified that additional blood samples for hematology testing (Days 8 and 22 for S-1 group; Day 8 for 5-FU group) are to be obtained during Cycles 1 through 8 or through the last cycle in which cisplatin is administered - Changed the timing of healthcare utilization assessment from Day 1 of each cycle to the end of the rest period of each cycle. - Modified text for consistency with respect to the timing of survival follow-up visits (every 8 weeks instead of every 2 months). - Removed the requirement to assess C-reactive protein. - Clarified the criterion for when an End-of-Treatment Visit is and is not required.
12 December 2011	- Revised Exclusion Criterion #1, which specified that all patients with only non-measurable lesions should be excluded was modified to allow patients with some types of non-measurable disease entry into the study - Increased the Baseline period during which CT scans for tumor measurement could be obtained from Day -28 through Day -4 to within 28 days prior to randomization. - Clarified Inclusion Criterion #2, which specified that patients should have unresectable tumors, to indicate that this applied only at the time of screening for study (i.e., patient may have had resectable tumor in the past). - Clarified Inclusion Criterion #5, which specified that patients should be able to take medications orally, to indicate that capsule contents should not be crushed or removed and given through a feeding tube. - Revised Inclusion Criterion #12 to clarify birth control requirements for both females and males. - Clarified, the dosing of 5-FU on Days 1 through 5 in Section 7.2.1. - Added the following drugs to the list of prohibited medications: nitroimidazoles, including metronidazole and misonidazole, methotrexate, and clozapine.
04 February 2014	- No patients would be randomized after 28 February 2014. - All patients would continue on study medication until any of the discontinuation criteria is met. - Patients currently enrolled would be followed until 6 months after randomization of the last patient. This allowed for an overall median follow-up time of approximately 22 months, which was at least twice as long as the target treatment median of 10 months. In addition, a 6- month minimum survival follow-up for all patients approximated the hypothesized control OS median. - The institutional site’s standard of care procedures would be followed, and study medication dosing, SAEs, and AEs related to medication discontinuation would be collected while the patient remained on treatment. Concomitant medications would only be reported if they were related to an SAE or AE related to medication discontinuation. Non-serious AEs leading to study drug discontinuation would be collected. These patients would be followed for 30 days after discontinuation from study treatment or the initiation of new anticancer therapy, whichever was earlier, after which there would be no follow-up.
03 May 2014	Changed the Sponsor’s name as of 01April 2014 from Taiho Pharmaceutical USA, Inc. (TPUI) to Taiho Oncology, Inc., and updated to add an additional Medical Monitor name and contact information for the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

As of 28 February 2014, the study was closed to slow accrual of enrollment. The decision was based on significant changes in the investigational and clinical practice landscape of frontline advanced gastric cancer (AGC).

Notes: