Clinical trial results:
Scheduling nab-paclItaxEl with GEmcitabine (SIEGE): Randomised phase II trial to investigate two different schedules of nab-paclitaxel (Abraxane) combined with gemcitabine as first line treatment for metastatic pancreatic ductal adenocarcinoma

Summary

EudraCT number	2013-001868-40
Trial protocol	GB
Global end of trial date	21 March 2018

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	
Summary attachment (see zip file)	SIEGE_AdverseEvents_listingbycategory (AE term category_for full report.pdf) Full SAE lisiting (SIEGE_FullSAEListing 22-Mar-17.xlsx)

Trial information

Trial identification

Sponsor protocol code	AX-PANC-PI-0101 (SIEGE)

Additional study identifiers

ISRCTN number	ISRCTN71070888
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS Project I.D.: 130640, UK REC Reference: 13/NI/0143

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
Sponsor organisation address	Hills Road , Cambridge , United Kingdom, CB2 0QQ
Public contact	Richard Skells, Cambridge Unversity Hospitals NHS Foundation Trust, +44 (0) 1223349707, richard.skells@addenbrookes.nhs.uk
Scientific contact	Pippa Corrie , Cambridge Unversity Hospitals NHS Foundation Trust, +44 (0) 1223349707, pippa.corrie@addenbrookes.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2017
Global end of trial reached?	Yes
Global end of trial date	21 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to investigate the outcome of sequential administration of nab-paclitaxel (Abraxane) combined with gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma (PDAC) in terms of progression-free survival.

Protection of trial subjects:

The study was approved by a Research Ethics Committee and received authorisation from the Medicines and Healthcare Products Regulatory Agency. Patients received verbal and written information prior to consenting to the trial and had the time to consider their participation and opportunity to ask questions. Patient data and samples were anonymised so that their information was kept confidential.

The SIEGE Protocol mandated the use of white blood cell growth factors (G-CSF) after every episode of Febrile Neutropenia, and was recommended for patients in episodes of higher grade neutropenia. Furthermore, dose modifications were also mandated for patients with hematological and non-hematological toxicities depending on the event, and the grade of such event, as detailed in the study Protocol. Particular guidance was given regarding Hepatic Impairment and Peripheral Neuropathy events, in line with the nab-paclitaxel Reference Safety Information. Any occurrence of life-threatening toxicity or hypersensitivity reaction mandated immediate discontinuation from treatment. Grade 4 non-hematological toxicity also mandated discontinuation from treatment, unless the investigator deemed that the patient continued to benefit from the treatment.

Serious Adverse Events were routinely reviewed by Sponsor and the ISDMC to ensure that all sites provided adequate supportive therapies when required and were compliant with the safety aspects of the SIEGE trial Protocol.

Background therapy:

Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) carries a poor prognosis. Gemcitabine (GEM) is the international standard of care. Combination therapy with FOLFIRINOX has previous demonstrated a superior progression-free survival, compared to GEM alone. However the side effects associated with this combination means that is may not be suitable for all mPDAC patients.

Nab-paclitaxel (Abraxane or ABX) is an albumin-bound formulation of paclitaxel. PDAC is well recognised to be a stromal-rich tumour which expresses high amounts of secreted protein acidic and rich in cysteine (SPARC); SPARC may act as an albumin-binding protein capable of sequestering ABX to concentrate the drug intratumourally. Previous trials using a combination therapy of ABX and GEM reported lower levels of neutropenia than with FOLFIRINOX, and generally appeared to be more widely tolerated

Evidence for comparator:

Whilst the interaction between Abraxane and Gemcitabine is not clear, studies in mouse models of PDAC suggest that delivery of ABX 24 hours prior to GEM might result in higher intra-tumoural GEM concentrations. Thus, scheduling of these two drugs may be critical to optimising clinical benefit.

Actual start date of recruitment	23 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 146
Worldwide total number of subjects	146
EEA total number of subjects	146

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)	69
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

146 participants were recruited between 24th March 2014 and 23rd March 2016 across 19 UK sites. Recruitment was steady and consistent throughout, with the recruitment half-way point achieved in March 2015 as expected.

Pre-assignment

Screening details:

186 Patients consented to the trial with suspected metastatic pancreatic adenocarcinoma deemed fit to treat.
40 Screen Failures. 34 deemed ineligible (13 pathological, 11 lab criteria, 10 poor performance) and 6 patients declined (2 declined biopsy, 2 travel, 1 alternative treatment and 1 no treament)
146 Patients were randomised

Pre-assignment period milestones

Number of subjects started	186[1]
Number of subjects completed	146

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 34
Reason: Number of subjects	Patient Decision: 6

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: Included in this number is the patients consented and screened in the study. Only 146 patients were enrolled in the study.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A - not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Concomitant

Arm description:

Patients on the control (concomitant) arm received intravenous nab-paclitaxel at 125mg/m2 immediately followed by intravenous gemcitabine at 1000mg/m2 on Days 1, 8 and 15 of a 4-weekly cycle for 6 cycles. Research bloods were taken from these patients on Cycle 1 Day 1, 8 and 15 in the first instance, and then on Day 1 of each subsequent cycle.

Arm type	Active comparator
Investigational medicinal product name	nab-Paclitaxel
Investigational medicinal product code	ABX
Other name	Abraxane
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients on the control (concomitant) arm received intravenous nab-paclitaxel at 125mg/m2 immediately followed by intravenous gemcitabine at 1000mg/m2 on Days 1, 8 and 15 of a 4-weekly cycle for 6 cycles.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	GEM
Other name	Gemzar
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients on the control (concomitant) arm received intravenous nab-paclitaxel at 125mg/m2 immediately followed by intravenous gemcitabine at 1000mg/m2 on Days 1, 8 and 15 of a 4-weekly cycle for 6 cycles. Research bloods were taken from these patients on Cycle 1 Day 1, 8 and 15 in the first instance, and then on Day 1 of each subsequent cycle.

Arm title	Sequential

Arm description:

Patient on the research (sequential) arm received intravenous nab-paclitaxel at 125mg/m2 on Day 1, 8 and 15, and intravenous gemcitabine at 1000mg/m2 on Day 2, 9 and 16 of a 4-weekly cycle for 6 cycles. Research bloods were taken from these patients on Cycle 1 Day 1, 2, 8, 9, 15 and 16 in the first instance, and then on Day 1 of each subsequent cycle.

Arm type	Experimental
Investigational medicinal product name	nab-Paclitaxel
Investigational medicinal product code	ABX
Other name	Abraxane
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patient on the research (sequential) arm received intravenous nab-paclitaxel at 125mg/m2 on Day 1, 8 and 15, and intravenous gemcitabine at 1000mg/m2 on Day 2, 9 and 16 of a 4-weekly cycle for 6 cycles.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	GEM
Other name	Gemzar
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patient on the research (sequential) arm received intravenous nab-paclitaxel at 125mg/m2 on Day 1, 8 and 15, and intravenous gemcitabine at 1000mg/m2 on Day 2, 9 and 16 of a 4-weekly cycle for 6 cycles.

Number of subjects in period 1	Concomitant	Sequential	
Started	75	71	
Completed	21	30	
Not completed	54	41	
Protocol deviation	1	1	
Death	6	3	
Patient Decision	4	2	
Adverse event, non-fatal	20	22	
Progressive Disease	23	11	
Consent withdrawn by subject	-	2	

Baseline characteristics

Reporting groups	
Reporting group title	Concomitant
Reporting group description:	
Patients on the control (concomitant) arm received intravenous nab-paclitaxel at 125mg/m2 immediately followed by intravenous gemcitabine at 1000mg/m2 on Days 1, 8 and 15 of a 4-weekly cycle for 6 cycles. Research bloods were taken from these patients on Cycle 1 Day 1, 8 and 15 in the first instance, and then on Day 1 of each subsequent cycle.	
Reporting group title	Sequential
Reporting group description:	
Patient on the research (sequential) arm received intravenous nab-paclitaxel at 125mg/m2 on Day 1, 8 and 15, and intravenous gemcitabine at 1000mg/m2 on Day 2, 9 and 16 of a 4-weekly cycle for 6 cycles. Research bloods were taken from these patients on Cycle 1 Day 1, 2, 8, 9, 15 and 16 in the first instance, and then on Day 1 of each subsequent cycle.	

Reporting group values	Concomitant	Sequential	Total
Number of subjects	75	71	146
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
all patients randomised			
Units: years			
median	67.1	63.4	
full range (min-max)	48.0 to 82.3	44.8 to 76.8	-
Gender categorical			
all patients randomised			
Units: Subjects			
Female	35	28	63
Male	40	43	83
Site of Primary Disease			
all patients randomised			
Units: Subjects			
Head	35	34	69
Body	19	20	39
Tail	21	17	38
Are Liver Metastases Present?			
all patients randomised			
Units: Subjects			
yes	62	60	122

no	13	11	24
Karnofsky Performance Status			
all patients randomised			
Units: Subjects			
70	6	11	17
80	19	20	39
90	33	22	55
100	17	18	35

End points

End points reporting groups

Reporting group title	Concomitant

Reporting group description:

Patients on the control (concomitant) arm received intravenous nab-paclitaxel at 125mg/m2 immediately followed by intravenous gemcitabine at 1000mg/m2 on Days 1, 8 and 15 of a 4-weekly cycle for 6 cycles. Research bloods were taken from these patients on Cycle 1 Day 1, 8 and 15 in the first instance, and then on Day 1 of each subsequent cycle.

Reporting group title	Sequential

Reporting group description:

Patient on the research (sequential) arm received intravenous nab-paclitaxel at 125mg/m2 on Day 1, 8 and 15, and intravenous gemcitabine at 1000mg/m2 on Day 2, 9 and 16 of a 4-weekly cycle for 6 cycles. Research bloods were taken from these patients on Cycle 1 Day 1, 2, 8, 9, 15 and 16 in the first instance, and then on Day 1 of each subsequent cycle.

Primary: Progression Free Survival

End point title	Progression Free Survival[1]

End point description:

Progression free survival (PFS) was calculated from date of randomisation to the date of clinical/radiological progression or death from any cause, whichever occurs first. CT scans were performed on an 8-weekly basis.

End point type	Primary

End point timeframe:

Patients were assessed every 4 weeks until disease progression. Patients were assessed 3-monthly after disease progression for a minimum of 1 year.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses to compare the two groups have been performed as the study is not powered to compare the arms.

End point values	Concomitant	Sequential		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75[2]	71[3]		
Units: months				
median (confidence interval 95%)	4.0 (3.0 to 5.4)	5.6 (3.6 to 7.2)		

Notes:

[2] - The observed 6-month PFS and median PFS was 32% in the concomitant arm

[3] - The observed 6-month PFS and median PFS was 46% in the sequential arm

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response

End point title	Objective Response

End point description:

measured according to RECIST V1.1

End point type	Secondary

End point timeframe:

Assessed 8-weekly from randomisation to disease progression

End point values	Concomitant	Sequential		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61[4]	56[5]		
Units: subjects				
Complete Response/Partial Response	19	29		
Stable Disease/Progressive Disease	42	27		

Notes:

[4] - 14 patients on the concomitant arm were not evaluable

[5] - 15 patient in the sequential arm were not evaluable.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety

End point description:

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment was reported. These events were reported as per the CTCAE v4.03 guidelines

End point type	Secondary

End point timeframe:

from date of informed consent to 30-days post-treatment

End point values	Concomitant	Sequential		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74[6]	68[7]		
Units: subjects				
Patients with Adverse Events Grade 3 and above	61	66		
Patients with Adverse Events Grade 1 -2	13	2		

Notes:

[6] - On the concomitant arm; 1 patient did not receive treatment; 193 G3+ AEs were reported.

[7] - On the sequential arm: 3 patients did not receive treatment; 314 G3+ AEs were reported.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AE's) reported were from the starting protocol treatment regimen until 30 days after the last administration of study drugs.

Adverse event reporting additional description:

Severity of all AE's has been reported as one of the secondary endpoints. Although a total of number of fatal AEs=15, the treatment related AE caused death = 7 (3 Concomitant, 4 Sequential).

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Sequential

Reporting group description: -

Reporting group title	Concomitant

Reporting group description: -

Serious adverse events	Sequential	Concomitant	
Total subjects affected by serious adverse events			
subjects affected / exposed	59 / 68 (86.76%)	48 / 74 (64.86%)	
number of deaths (all causes)	59	64	
number of deaths resulting from adverse events	10	5	
Vascular disorders			
Vascular disorders - Other, splenic artery pseudoaneurysm			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	3 / 68 (4.41%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical and medical procedures			

Surgical and medical procedures - Other, anorectal surgery			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	13 / 68 (19.12%)	13 / 74 (17.57%)	
occurrences causally related to treatment / all	1 / 16	2 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusion			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations - Other, hepatic enzyme increased			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			

subjects affected / exposed	7 / 68 (10.29%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	5 / 9	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations - Other, deranged liver function tests			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (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			
Febrile neutropenia			
subjects affected / exposed	10 / 68 (14.71%)	9 / 74 (12.16%)	
occurrences causally related to treatment / all	5 / 10	4 / 10	
deaths causally related to treatment / all	0 / 1	0 / 1	
Anemia			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnea			
subjects affected / exposed	3 / 68 (4.41%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 68 (2.94%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders - Other, lung abscess			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Stroke			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 68 (1.47%)	3 / 74 (4.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ascites			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to	0 / 1	0 / 0	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	2 / 68 (2.94%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jejunal obstruction			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal hemorrhage			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophagitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 68 (2.94%)	6 / 74 (8.11%)	
occurrences causally related to treatment / all	1 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric hemorrhage			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal obstruction			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal hemorrhage			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 68 (1.47%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Gallbladder obstruction			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders - Other, biliary obstruction			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders - Other, cholangitis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	

deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders - Other, jaundice and hepatorenal syndrome			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders - Other, biliary sepsis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatremia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anorexia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 68 (5.88%)	3 / 74 (4.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Biliary tract infection			
subjects affected / exposed	4 / 68 (5.88%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other, pneumonia			
subjects affected / exposed	1 / 68 (1.47%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 1	1 / 1	
Bronchial infection			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter related infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other, infection unknown			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations - Other, viral illness			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 68 (1.47%)	3 / 74 (4.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	4 / 68 (5.88%)	4 / 74 (5.41%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Skin infection			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory infection			
subjects affected / exposed	0 / 68 (0.00%)	2 / 74 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	5 / 68 (7.35%)	4 / 74 (5.41%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	

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

Non-serious adverse events	Sequential	Concomitant	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 68 (98.53%)	69 / 74 (93.24%)	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	7	

Hot flashes			
subjects affected / exposed	2 / 68 (2.94%)	2 / 74 (2.70%)	
occurrences (all)	2	2	
Hypertension			
subjects affected / exposed	4 / 68 (5.88%)	4 / 74 (5.41%)	
occurrences (all)	5	4	
Hypotension			
subjects affected / exposed	6 / 68 (8.82%)	4 / 74 (5.41%)	
occurrences (all)	10	4	
Superficial thrombophlebitis			
subjects affected / exposed	0 / 68 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	2	
Phlebitis			
subjects affected / exposed	0 / 68 (0.00%)	4 / 74 (5.41%)	
occurrences (all)	0	4	
Thromboembolic event			
subjects affected / exposed	8 / 68 (11.76%)	3 / 74 (4.05%)	
occurrences (all)	8	3	
Vascular disorders - Other, varicose vein pain			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Surgical and medical procedures - Other, elective stoma reversal			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Surgical and medical procedures - Other, wart removal			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Anaphylaxis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	52 / 68 (76.47%)	52 / 74 (70.27%)	
occurrences (all)	165	126	
Chills			
subjects affected / exposed	10 / 68 (14.71%)	6 / 74 (8.11%)	
occurrences (all)	16	7	
Flu like symptoms			
subjects affected / exposed	9 / 68 (13.24%)	10 / 74 (13.51%)	
occurrences (all)	21	16	
General disorders and administration site conditions - Other, Fall in performance status			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions - Other, fall in performance score			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Fever			
subjects affected / exposed	19 / 68 (27.94%)	14 / 74 (18.92%)	
occurrences (all)	29	19	
General disorders and administration site conditions - Other, common cold			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	2	1	
General disorders and administration site conditions - Other, drop in performance score			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Edema face			
subjects affected / exposed	1 / 68 (1.47%)	2 / 74 (2.70%)	
occurrences (all)	1	3	
Edema limbs			
subjects affected / exposed	22 / 68 (32.35%)	24 / 74 (32.43%)	
occurrences (all)	35	31	
Localized edema			

subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Infusion site extravasation			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Malaise			
subjects affected / exposed	2 / 68 (2.94%)	1 / 74 (1.35%)	
occurrences (all)	2	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 68 (0.00%)	3 / 74 (4.05%)	
occurrences (all)	0	4	
Pain			
subjects affected / exposed	3 / 68 (4.41%)	1 / 74 (1.35%)	
occurrences (all)	3	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 68 (1.47%)	2 / 74 (2.70%)	
occurrences (all)	1	2	
Anxiety			
subjects affected / exposed	3 / 68 (4.41%)	2 / 74 (2.70%)	
occurrences (all)	3	3	
Confusion			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	5 / 68 (7.35%)	2 / 74 (2.70%)	
occurrences (all)	5	3	
Restlessness			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders - Other, low mood			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	9 / 68 (13.24%)	7 / 74 (9.46%)	
occurrences (all)	9	9	

Suicidal ideation			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders - Other, lump			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Vaginal hemorrhage			
subjects affected / exposed	2 / 68 (2.94%)	1 / 74 (1.35%)	
occurrences (all)	2	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 68 (1.47%)	2 / 74 (2.70%)	
occurrences (all)	1	2	
Bruising			
subjects affected / exposed	0 / 68 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications - Other, wound			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications - small wounds on both arms			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Spinal fracture			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	10 / 68 (14.71%)	3 / 74 (4.05%)	
occurrences (all)	16	3	
Alanine aminotransferase increased			

subjects affected / exposed	10 / 68 (14.71%)	7 / 74 (9.46%)	
occurrences (all)	18	15	
Alkaline phosphatase increased			
subjects affected / exposed	7 / 68 (10.29%)	8 / 74 (10.81%)	
occurrences (all)	17	14	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 68 (5.88%)	0 / 74 (0.00%)	
occurrences (all)	4	0	
GGT increased			
subjects affected / exposed	4 / 68 (5.88%)	14 / 74 (18.92%)	
occurrences (all)	10	19	
Creatinine increased			
subjects affected / exposed	2 / 68 (2.94%)	2 / 74 (2.70%)	
occurrences (all)	3	2	
Electrocardiogram QT corrected interval prolonged			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
INR increased			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Investigations - Other, c-reactive protein increased			
subjects affected / exposed	4 / 68 (5.88%)	2 / 74 (2.70%)	
occurrences (all)	6	2	
Investigations - Other, creatinine decreased			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Investigations - Other, liver function test increased			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Investigations - Other, neutrophil count increased			
subjects affected / exposed	0 / 68 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	2	
Investigations - Other, platelet count			

increased			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	4	1	
Investigations - Other, transaminases increased			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	4	0	
Investigations - Other, urea increased			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Investigations - Other, white blood cell increased			
subjects affected / exposed	1 / 68 (1.47%)	2 / 74 (2.70%)	
occurrences (all)	1	2	
Lymphocyte count decreased			
subjects affected / exposed	1 / 68 (1.47%)	3 / 74 (4.05%)	
occurrences (all)	1	12	
Platelet count decreased			
subjects affected / exposed	14 / 68 (20.59%)	32 / 74 (43.24%)	
occurrences (all)	35	67	
Neutrophil count decreased			
subjects affected / exposed	45 / 68 (66.18%)	30 / 74 (40.54%)	
occurrences (all)	136	60	
Weight loss			
subjects affected / exposed	5 / 68 (7.35%)	5 / 74 (6.76%)	
occurrences (all)	5	5	
Weight gain			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
White blood cell decreased			
subjects affected / exposed	12 / 68 (17.65%)	12 / 74 (16.22%)	
occurrences (all)	40	25	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders - Other,			

tachycardia of unknown origin.			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			
subjects affected / exposed	3 / 68 (4.41%)	2 / 74 (2.70%)	
occurrences (all)	3	3	
Palpitations			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Sinus bradycardia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 68 (22.06%)	5 / 74 (6.76%)	
occurrences (all)	19	6	
Hiccups			
subjects affected / exposed	3 / 68 (4.41%)	5 / 74 (6.76%)	
occurrences (all)	7	9	
Epistaxis			
subjects affected / exposed	3 / 68 (4.41%)	9 / 74 (12.16%)	
occurrences (all)	3	9	
Dyspnea			
subjects affected / exposed	15 / 68 (22.06%)	17 / 74 (22.97%)	
occurrences (all)	19	24	
Hypoxia			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders - Other, coryzal symptoms			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders - Other, haemoptysis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal			

disorders - Other, rhinorrhoea			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Hoarseness			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Sinus disorder			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Sore throat			
subjects affected / exposed	7 / 68 (10.29%)	2 / 74 (2.70%)	
occurrences (all)	7	2	
Pleural effusion			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Postnasal drip			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	6 / 68 (8.82%)	3 / 74 (4.05%)	
occurrences (all)	7	5	
Wheezing			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Pneumonitis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Voice alteration			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders - Other, Blood tinged secretions			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	

occurrences (all)	0	1	

Blood and lymphatic system disorders			
Blood and lymphatic system disorders - Other, pancytopenia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Febrile neutropenia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Anemia			
subjects affected / exposed	31 / 68 (45.59%)	31 / 74 (41.89%)	
occurrences (all)	109	65	
Nervous system disorders			
Aphonia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	7 / 68 (10.29%)	5 / 74 (6.76%)	
occurrences (all)	10	6	
Dysarthria			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Dysesthesia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	11 / 68 (16.18%)	8 / 74 (10.81%)	
occurrences (all)	12	9	
Headache			
subjects affected / exposed	4 / 68 (5.88%)	6 / 74 (8.11%)	
occurrences (all)	5	8	
Lethargy			
subjects affected / exposed	14 / 68 (20.59%)	7 / 74 (9.46%)	
occurrences (all)	29	10	
Nervous system disorders - Other, footdrop			

subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Nervous system disorders - Other, posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Paresthesia			
subjects affected / exposed	4 / 68 (5.88%)	4 / 74 (5.41%)	
occurrences (all)	5	6	
Somnolence			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Nervous system disorders - Other, reduced sensation			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Neuralgia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Tremor			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Peripheral sensory neuropathy			
subjects affected / exposed	20 / 68 (29.41%)	20 / 74 (27.03%)	
occurrences (all)	32	34	
Peripheral motor neuropathy			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences (all)	4	0	
Vasovagal reaction			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	

occurrences (all)	1	0	

Eye disorders			
Eye pain			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Flashing lights			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences (all)	3	0	
Eye disorders - Other, sticky eye			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Eye disorders - Other, vision change			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Eye disorders - Other, conjunctival haemorrhage			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Eye disorders - Other, bloodshot eye			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Eye disorders - Other, conjuctival hemorrhage			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear and labyrinth disorders - Other, blocked ear			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
External ear inflammation			

subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	2 / 68 (2.94%)	1 / 74 (1.35%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Bloating			
subjects affected / exposed	5 / 68 (7.35%)	3 / 74 (4.05%)	
occurrences (all)	8	4	
Abdominal distension			
subjects affected / exposed	2 / 68 (2.94%)	1 / 74 (1.35%)	
occurrences (all)	2	1	
Abdominal pain			
subjects affected / exposed	24 / 68 (35.29%)	24 / 74 (32.43%)	
occurrences (all)	35	34	
Anal pain			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	
Flatulence			
subjects affected / exposed	3 / 68 (4.41%)	1 / 74 (1.35%)	
occurrences (all)	3	1	
Gastroesophageal reflux disease			
subjects affected / exposed	5 / 68 (7.35%)	1 / 74 (1.35%)	
occurrences (all)	5	2	
Gastrointestinal disorders - Other, dry lips			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Ascites			
subjects affected / exposed	3 / 68 (4.41%)	5 / 74 (6.76%)	
occurrences (all)	3	6	
Gastrointestinal disorders - Other, pneumatosis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders - Other, oral thrush			
subjects affected / exposed	7 / 68 (10.29%)	1 / 74 (1.35%)	

occurrences (all)	8	1	
Gastrointestinal disorders - Other, right inguinal hernia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders - Other, tenesmus			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders - Other, steatorrhea			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	6 / 68 (8.82%)	3 / 74 (4.05%)	
occurrences (all)	6	4	
Dysphagia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Colitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Hemorrhoidal hemorrhage			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Hemorrhoids			
subjects affected / exposed	2 / 68 (2.94%)	2 / 74 (2.70%)	
occurrences (all)	2	2	
Constipation			
subjects affected / exposed	29 / 68 (42.65%)	26 / 74 (35.14%)	
occurrences (all)	42	36	
Gastrointestinal disorders - Other, oedematous bowel			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Diarrhea			
subjects affected / exposed	34 / 68 (50.00%)	34 / 74 (45.95%)	
occurrences (all)	83	70	

Dyspepsia			
subjects affected / exposed	5 / 68 (7.35%)	1 / 74 (1.35%)	
occurrences (all)	5	1	
Obstruction gastric			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Rectal hemorrhage			
subjects affected / exposed	2 / 68 (2.94%)	1 / 74 (1.35%)	
occurrences (all)	3	2	
Mucositis oral			
subjects affected / exposed	31 / 68 (45.59%)	22 / 74 (29.73%)	
occurrences (all)	55	32	
Oral pain			
subjects affected / exposed	2 / 68 (2.94%)	3 / 74 (4.05%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	36 / 68 (52.94%)	35 / 74 (47.30%)	
occurrences (all)	86	58	
Toothache			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	34 / 68 (50.00%)	23 / 74 (31.08%)	
occurrences (all)	51	38	
Stomach pain			
subjects affected / exposed	0 / 68 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	2	
Hepatobiliary disorders			
Hepatobiliary disorders - Other, cholangitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders - Other, ductal obstruction			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences (all)	3	0	
Cystitis noninfective			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Chronic kidney disease			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Hematuria			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Renal and urinary disorders - Other, dysuria			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Urinary frequency			
subjects affected / exposed	3 / 68 (4.41%)	0 / 74 (0.00%)	
occurrences (all)	3	0	
Urinary tract pain			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Urinary urgency			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	33 / 68 (48.53%)	26 / 74 (35.14%)	
occurrences (all)	51	37	
Hyperhidrosis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	2	
Dry skin			
subjects affected / exposed	6 / 68 (8.82%)	5 / 74 (6.76%)	

occurrences (all)	7	5	
Erythema multiforme			
subjects affected / exposed	2 / 68 (2.94%)	4 / 74 (5.41%)	
occurrences (all)	4	5	
Skin and subcutaneous tissue disorders - Other, changes to skin of eye			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Rash acneiform			
subjects affected / exposed	5 / 68 (7.35%)	4 / 74 (5.41%)	
occurrences (all)	10	7	
Rash maculo-papular			
subjects affected / exposed	18 / 68 (26.47%)	8 / 74 (10.81%)	
occurrences (all)	21	13	
Scalp pain			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders - Other, bleeding of forehead cut			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders - Other, boil			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	8 / 68 (11.76%)	7 / 74 (9.46%)	
occurrences (all)	8	11	
Skin and subcutaneous tissue disorders - Other, foot corn			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders - Other, nail pain			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders - Other, rash			

subjects affected / exposed	1 / 68 (1.47%)	2 / 74 (2.70%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders - Other, red spots			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders - Other, wart			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Skin ulceration			
subjects affected / exposed	2 / 68 (2.94%)	2 / 74 (2.70%)	
occurrences (all)	2	2	
Nail loss			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders - Other, cutaneous toxicity			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	3	0	
Pain of skin			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	5 / 68 (7.35%)	0 / 74 (0.00%)	
occurrences (all)	7	0	
Nail discoloration			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	3 / 68 (4.41%)	0 / 74 (0.00%)	
occurrences (all)	4	0	
Purpura			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders - Other, erythema			

subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	2	1	
Skin hyperpigmentation			
subjects affected / exposed	3 / 68 (4.41%)	1 / 74 (1.35%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 68 (5.88%)	7 / 74 (9.46%)	
occurrences (all)	4	9	
Arthritis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	11 / 68 (16.18%)	10 / 74 (13.51%)	
occurrences (all)	16	12	
Bone pain			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Generalized muscle weakness			
subjects affected / exposed	4 / 68 (5.88%)	2 / 74 (2.70%)	
occurrences (all)	6	2	
Myalgia			
subjects affected / exposed	5 / 68 (7.35%)	5 / 74 (6.76%)	
occurrences (all)	7	8	
Muscle weakness lower limb			
subjects affected / exposed	3 / 68 (4.41%)	2 / 74 (2.70%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders - Other, cachexia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders - Other, groin pain			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Joint effusion			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	

occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders - Other, myoclonic Jerks			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders - Other, rib pain			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders - Other, shoulder pain			
subjects affected / exposed	3 / 68 (4.41%)	1 / 74 (1.35%)	
occurrences (all)	3	1	
Musculoskeletal and connective tissue disorders - Other, stiffness in legs			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	4	0	
Neck pain			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	7 / 68 (10.29%)	7 / 74 (9.46%)	
occurrences (all)	9	8	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	25 / 68 (36.76%)	25 / 74 (33.78%)	
occurrences (all)	65	36	
Dehydration			
subjects affected / exposed	5 / 68 (7.35%)	0 / 74 (0.00%)	
occurrences (all)	5	0	
Hyperglycemia			
subjects affected / exposed	2 / 68 (2.94%)	1 / 74 (1.35%)	
occurrences (all)	3	1	
Hyperkalemia			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences (all)	3	0	

Hypoalbuminemia			
subjects affected / exposed	12 / 68 (17.65%)	3 / 74 (4.05%)	
occurrences (all)	19	8	
Hypocalcemia			
subjects affected / exposed	4 / 68 (5.88%)	4 / 74 (5.41%)	
occurrences (all)	9	5	
Hypokalemia			
subjects affected / exposed	5 / 68 (7.35%)	3 / 74 (4.05%)	
occurrences (all)	11	4	
Hypomagnesemia			
subjects affected / exposed	3 / 68 (4.41%)	1 / 74 (1.35%)	
occurrences (all)	3	1	
Hyponatremia			
subjects affected / exposed	3 / 68 (4.41%)	5 / 74 (6.76%)	
occurrences (all)	3	6	
Hypophosphatemia			
subjects affected / exposed	1 / 68 (1.47%)	1 / 74 (1.35%)	
occurrences (all)	1	2	
Infections and infestations			
Eye infection			
subjects affected / exposed	2 / 68 (2.94%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Gum infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Catheter related infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Device related infection			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Infections and infestations - Other, finger infection			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Infections and infestations - Other, infected toe			

subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Infections and infestations - Other, infection unknown			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Infections and infestations - Other, Insect bite to right forearm			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Infections and infestations - Other, line infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Infections and infestations - Other, oral infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Infections and infestations - Other, oral thrush			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Infections and infestations - Other, pneumonia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Infections and infestations - Other, pseudomonas aeruginosa infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Infections and infestations - Other, shingles			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Sepsis			
subjects affected / exposed	1 / 68 (1.47%)	2 / 74 (2.70%)	
occurrences (all)	1	2	
Lip infection			
subjects affected / exposed	3 / 68 (4.41%)	2 / 74 (2.70%)	
occurrences (all)	3	2	

Mucosal infection			
subjects affected / exposed	1 / 68 (1.47%)	4 / 74 (5.41%)	
occurrences (all)	1	4	
Papulopustular rash			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Skin infection			
subjects affected / exposed	6 / 68 (8.82%)	2 / 74 (2.70%)	
occurrences (all)	9	2	
Nail infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Small intestine infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Lung infection			
subjects affected / exposed	11 / 68 (16.18%)	3 / 74 (4.05%)	
occurrences (all)	13	3	
Vaginal infection			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	2 / 68 (2.94%)	2 / 74 (2.70%)	
occurrences (all)	2	2	
Penile infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Upper respiratory infection			
subjects affected / exposed	7 / 68 (10.29%)	2 / 74 (2.70%)	
occurrences (all)	9	2	
Urinary tract infection			
subjects affected / exposed	6 / 68 (8.82%)	4 / 74 (5.41%)	
occurrences (all)	6	4	
Pharyngitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	

Wound infection subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	0 / 74 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2014	Addition of new dose modifications, safety information for Abraxane and Gemcitabine combination therapy, new sites and changes to PI
27 January 2015	Clarification of dose delay timelines, clarification of eligibility criteria, addition of instructions for treating patients with hepatic impairment and change to team contact details
14 October 2015	Increase of recruitment total from 120 patients to 146 patients, clarification of statistical analysis plan and calculation of sample size in accordance with the evaluable patient criteria.
04 January 2016	Changes to the patient information sheet and protocol - including change to number of participating sites, number of patients on each arm required to assess end points, clarification of the inclusion criterion addressing the provision of tumour samples, clarification of IMP SmPC-particulate matter, clarification of the rules regarding dose escalation, change to the requirements for the follow-up assessments

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported