Clinical trial results:
Pancreatic Resectability in Cancers with Known Limited Extension (PRICKLE) - A single-centre phase 2a study of Gemcitabine plus Nab-paclitaxel for borderline unresectable locally advanced pancreatic cancer.

Summary

EudraCT number	2013-004200-19
Trial protocol	GB
Global end of trial date	26 October 2017

Results information

Result version number	v1 (current)
This version publication date	11 November 2018
First version publication date	11 November 2018

Trial information

Trial identification

Sponsor protocol code	PRICKLE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02124369
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
Sponsor organisation address	Hills Road, Cambridge, United Kingdom, CB2 0QQ
Public contact	Carrie Bayliss, Cambridge Unversity Hospitals NHS Foundation Trust, 44 01223348158, cctu@addenbrookes.nhs.uk
Scientific contact	Carrie Bayliss, Cambridge Unversity Hospitals NHS Foundation Trust, 44 01223348158, cctu@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	01 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2017
Global end of trial reached?	Yes
Global end of trial date	26 October 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine efficacy of ABX/GEM in downstaging “category 2” borderline unresectable locally advanced pancreatic cancer tumours sufficiently to enable resection.

Protection of trial subjects:

The study was approved by a Research Ethics Committee and received authorisation from the Medicines and Healthcare Products Regulatory Authority. Patients received verbal and written information prior consenting to the trial, and had time to consider their participation and opportunity to ask questions. Consenting patients had a series of screening tests and exams to ensure they were suitable for the study and it was safe to proceed. Enrolment into the trial did not affect any aspect of the surgical treatment plan and each patient was treated according to local practice. On registration to the trial patients were allocated a unique reference number to be used on all data and samples sent to the sponsor, which allowed their personal data to remain anonymous. Only the patients direct care team had access to their recruited participants personal data during the trial. Patients could be withdrawn at any time, at the patient's request or at the clinician's decision. Adverse events were monitored on an ongoing basis, with end of study assessments performed approx 28-35 days after the end of study drug administration or post-surgery.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	12 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 9
Worldwide total number of subjects	9
EEA total number of subjects	9

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)	4
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The sample size for the trial was a maximum of 17 evaluable patients. 9 patients were registered into the trial.

Pre-assignment

Screening details:

Patients aged >= 18 years with borderline unresectable advanced pancreatic adenocarcinoma, defined as Cat 2 by central radiological review, histological/cytological diagnosis, ECOG PS 0/1. A total of 23 patients consented to the trial, with 14 screen failures. The first patient was enrolled on 27 Aug 2014 and the last enrolled on 10 Apr 2017.

Pre-assignment period milestones

Number of subjects started	23[1]
Number of subjects completed	9

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not meet Inc/Exc criteria: 14

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: Worldwide number enrolled in the trial is the number of consented subjects meeting inclusion/exclusion criteria and who were registered into the study to receive treatment. The number of subjects who started the pre-assignment period is the number of consented subjects screened for eligibility.

Period 1

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

Arms

Arm title	Abraxane & Gemcitabine treatment

Arm description:

Patients received Abraxane followed by Gemcitabine in combination for up to 6 cycles. Evaluation of resectability was performed after 3 cycles. If operable after 3 cycles, appropriate surgical intervention was undertaken. 1 further cycle of treatment could be administered whilst patients awaited surgery. If patients were considered unresectable after 3 cycles, a further 3 cycles of treatment was given before final re-evaluation of resectability. Patients received up to a maximum of 6 cycles.

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

Dosage and administration details:

Abraxane was administered at a dose of 125mg/m2 intravenously over 30 minutes on Days 1, 8 and 15 of each 28-day cycle, for a minimum of 3 cycles and a maximum of 6 cycles.

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

Dosage and administration details:

Gemcitabine was administered at a dose of 1000mg/m2 intravenously over 30 minutes immediately after the completion of Abraxane administration on Days 1, 8 and 15 of each 28-day cycle. Patients received a minimum of 3 cycles and a maximum of 6 cycles.

Number of subjects in period 1	Abraxane & Gemcitabine treatment
Started	9
Completed	9

Period 2

Period 2 title	Post-Baseline
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Abraxane & Gemcitabine treatment

Arm description:

Patients received Abraxane followed by Gemcitabine in combination for up to 6 cycles. Evaluation of resectability was performed after 3 cycles. If operable after 3 cycles, appropriate surgical intervention was undertaken. 1 further cycle of treatment could be administered whilst patients awaited surgery. If patients were considered unresectable after 3 cycles, a further 3 cycles of treatment was given before final re-evaluation of resectability. Patients received up to a maximum of 6 cycles.

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

Dosage and administration details:

Abraxane was administered at a dose of 125mg/m2 intravenously over 30 minutes on Days 1, 8 and 15 of each 28-day cycle, for a minimum of 3 cycles and a maximum of 6 cycles.

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

Dosage and administration details:

Gemcitabine was administered at a dose of 1000mg/m2 intravenously over 30 minutes immediately after the completion of Abraxane administration on Days 1, 8 and 15 of each 28-day cycle. Patients received a minimum of 3 cycles and a maximum of 6 cycles.

Number of subjects in period 2	Abraxane & Gemcitabine treatment
Started	9
Completed	9

Baseline characteristics

Reporting groups	
Reporting group title	On study
Reporting group description:	
All enrolled subjects	

Reporting group values	On study	Total	
Number of subjects	9	9	
Age categorical			
All enrolled subjects			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	4	4	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous			
Units: years			
median	65.5		
full range (min-max)	59.0 to 77.3	-	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	3	3	
Stage at Initial Diagnosis of PDAC			
Stage at Initial Diagnosis of Pancreatic Ductal Adenocarcinoma (PDAC)			
Units: Subjects			
II	1	1	
IIB	2	2	
III	6	6	
ECOG PS			
ECOG Performance Status			
Units: Subjects			
PS 0	5	5	
PS 1	4	4	
CA19.9			
Units: U/ml			
median	432.00		
full range (min-max)	165.00 to 1334.00	-	

Subject analysis sets

Subject analysis set title	Abraxane & Gemcitabine treatment (Evaluable)
Subject analysis set type	Full analysis

Subject analysis set description:

The Evaluable population is defined as patients who received at least 3 cycles and up to 6 cycles of protocol treatment or stopped protocol treatment early due to disease progression. The evaluable population is used for the analysis of the primary endpoint.

Reporting group values	Abraxane & Gemcitabine treatment (Evaluable)		
Number of subjects	9		
Age categorical			
All enrolled subjects			
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)	4		
From 65-84 years	5		
85 years and over	0		
Age continuous			
Units: years			
median	65.5		
full range (min-max)	59.0 to 77.3		
Gender categorical			
Units: Subjects			
Female	6		
Male	3		
Stage at Initial Diagnosis of PDAC			
Stage at Initial Diagnosis of Pancreatic Ductal Adenocarcinoma (PDAC)			
Units: Subjects			
II	1		
IIB	2		
III	6		
ECOG PS			
ECOG Performance Status			
Units: Subjects			
PS 0	5		
PS 1	4		
CA19.9			
Units: U/ml			
median	432.00		
full range (min-max)	165.00 to 1334.00		

End points

End points reporting groups

Reporting group title	Abraxane & Gemcitabine treatment

Reporting group description:

Patients received Abraxane followed by Gemcitabine in combination for up to 6 cycles. Evaluation of resectability was performed after 3 cycles. If operable after 3 cycles, appropriate surgical intervention was undertaken. 1 further cycle of treatment could be administered whilst patients awaited surgery. If patients were considered unresectable after 3 cycles, a further 3 cycles of treatment was given before final re-evaluation of resectability. Patients received up to a maximum of 6 cycles.

Reporting group title	Abraxane & Gemcitabine treatment

Reporting group description:

Patients received Abraxane followed by Gemcitabine in combination for up to 6 cycles. Evaluation of resectability was performed after 3 cycles. If operable after 3 cycles, appropriate surgical intervention was undertaken. 1 further cycle of treatment could be administered whilst patients awaited surgery. If patients were considered unresectable after 3 cycles, a further 3 cycles of treatment was given before final re-evaluation of resectability. Patients received up to a maximum of 6 cycles.

Subject analysis set title	Abraxane & Gemcitabine treatment (Evaluable)
Subject analysis set type	Full analysis

Subject analysis set description:

The Evaluable population is defined as patients who received at least 3 cycles and up to 6 cycles of protocol treatment or stopped protocol treatment early due to disease progression. The evaluable population is used for the analysis of the primary endpoint.

Primary: Determination of resectability rate in "category 2" borderline unresectable locally advanced pancreatic cancer patients after up to 6 cycles of treatment with Abraxane and Gemcitabine as deemed by independent review

End point title	Determination of resectability rate in "category 2" borderline unresectable locally advanced pancreatic cancer patients after up to 6 cycles of treatment with Abraxane and Gemcitabine as deemed by independent review

End point description:

Evaluation of resectability occurred through central review of CT scans; patients enrolled on study with Category 2 tumours were only to be considered resectable if their CT scan confirmed change to Category 1 characteristics. Each assessment of operability was undertaken by at least two external observers from a pre-specified panel of surgeons and radiologists using a structured reporting system.
All 9 enrolled subjects are in the Evaluable population, hence they are all included in the primary endpoint analysis.
This is a single arm study, therefore there are no statistical comparisons.
A total of 4/9 (44.4%) subjects were considered resectable by central radiological review at end of treatment (95% CI: 13.7%, 78.8%).

End point type	Primary

End point timeframe:

If rendered operable after 3 or 6 cycles, appropriate surgical intervention was undertaken and patients went on to standard adjuvant therapy. For patients who were resectable after 3 cycles, 1 further cycle could be administered whilst awaiting surgery

End point values	Abraxane & Gemcitabine treatment	Abraxane & Gemcitabine treatment (Evaluable)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	9		
Units: Subjects				
Resectable	4	4		
Non-Resectable	5	5		

Statistical analyses

Statistical analysis title	resection rate

Statistical analysis description:

single-armed estimate and 95% CI of resection rate

Comparison groups	Abraxane & Gemcitabine treatment v Abraxane & Gemcitabine treatment (Evaluable)
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	rate
Point estimate	0.444
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.137
upper limit	0.788

Notes:

[1] - This is a single arm study, a total of 9 patients were enrolled. However the "Number of subjects included in analysis = 18" (two rows above) is an incorrect value, auto-generated which combines the "Reporting group" and "Subject analysis set".

Secondary: Radiological response as determined by percentage change in sum of longest diameters for all target lesions at 3 or 6 months from the start of treatment

End point title	Radiological response as determined by percentage change in sum of longest diameters for all target lesions at 3 or 6 months from the start of treatment

End point description:

This is a single arm study, therefore there are no statistical comparisons.
Summary statistics for Percentage Change from Baseline are presented.

End point type	Secondary

End point timeframe:

Percentage change in the sum of the longest diameters for all target lesions at 3 or 6 months from start of ABX/GEM treatment.

End point values	Abraxane & Gemcitabine treatment (Evaluable)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: mm				
median (full range (min-max))	-14.3 (-46.7 to 0.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response assessment by RECIST 1.1 criteria using conventional computerised tomography (CT) or magnetic resonance imaging (MRI) measurements

End point title	Response assessment by RECIST 1.1 criteria using conventional computerised tomography (CT) or magnetic resonance imaging (MRI) measurements

End point description:

This is a single-arm study, therefore there are no statistical comparisons.
Responder is defined as Overall response = CR or PR.
A total of 3/9 (33.3%) subjects were considered an Overall Responder at end of treatment (95% CI: 7.5%, 70.1%).

End point type	Secondary

End point timeframe:

Response Assessments (CR, PR, SD or PD) by RECIST 1.1 criteria at 3 or 6 months using conventional CT or MRI.

End point values	Abraxane & Gemcitabine treatment (Evaluable)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: Subjects				
Responder (CR/PR)	3			
Non-Responder (SD/PD/NE)	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Biochemical response rate (serum CA19.9)

End point title	Biochemical response rate (serum CA19.9)

End point description:

This is a single-arm study, therefore there are no statistical comparisons.

Evaluable subjects who have data at Baseline and End of Treatment visit are included.
Summary statistics for Percentage Change from Baseline are presented.

End point type	Secondary

End point timeframe:

Baseline is defined as the Day 1 Cycle 1 assessment. End of Treatment visit occurred 30 (28-35) days following end of treatment, or 30 (28-35) days following date of surgery for subjects undergoing surgery.

End point values	Abraxane & Gemcitabine treatment (Evaluable)			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: U/ml				
median (full range (min-max))	-81.19 (-95.14 to -33.33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Operability Rate (Institution determined)

End point title	Operability Rate (Institution determined)

End point description:

Primary Endpoint of resectability after up to 6 cycles is based on independent central review. If local site assessment of disease at the Specialist Multi-Disciplinary Team contradicted the independent assessment such that local investigators decided an R0 resection was possible, this is captured in this secondary endpoint of operability rate.
This is a single-arm study, therefore there are no statistical comparisons.
A total of 5/9 (55.6%) subjects were considered resectable by local review at end of treatment (95% CI: 21.2%, 86.3%).
Note that the LOCAL and CENTRAL review decisions differed for 3 subjects: 2 subjects were not considered resectable based on central review but were considered operable based on local review, and both underwent surgery; 1 subject was considered resectable based on central review but not considered operable based on local review, this subject underwent surgery. Therefore, a total of 6 subjects were actually considered eligible for surgery.

End point type	Secondary

End point timeframe:

Operability rate is based on the local radiological review outcome after up to 6 cycles of ABX/GEM treatment.

End point values	Abraxane & Gemcitabine treatment (Evaluable)			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: Subjects				
Resectable	5			
Non-resectable	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Pathological down-staging and margin status after resection

End point title	Pathological down-staging and margin status after resection

End point description:

This is a single-arm study, therefore there are no statistical comparisons.
The percentage of patients in each category of tumour destruction is presented. The categories range from Grade I (1%-9% of tumour necrosis) to Grade IV (absence of viable tumour cells), with an additional category of None (no tumour necrosis).
Whilst 6 subjects initially underwent surgery, for one subject their surgery was unable to be performed (peritoneal deposits), and they have no histopathology report.
Of the 5 subjects with Histopathology Report, 4 (80%) had resection margins involved.

End point type	Secondary

End point timeframe:

As captured on Histopathology Report following Surgery.

End point values	Abraxane & Gemcitabine treatment (Evaluable)			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: Subjects				
Grade I (1%-9% of tumour necrosis)	2			
Grade II (10%-90% of tumour necrosis)	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of peri- and post-operative outcomes following surgery

End point title	Assessment of peri- and post-operative outcomes following surgery

End point description:

This is a single-arm study, therefore there are no statistical comparisons.
Intra-operative complications were reported for 1 subject (prolonged procedure due to vascular

involvement).
Specific post-operative complications of Delayed gastric emptying / post-operative pancreatic fistula / post-operative pancreatic haemorrhage / any other post-operative complications were captured at the Surgery follow-up visit. There were none reported.

End point type	Secondary

End point timeframe:

Intra-operative complications were captured on the Surgery CRF.
Post-operative complications were reported at the Day of Surgery + 2-6 weeks visit.

End point values	Abraxane & Gemcitabine treatment (Evaluable)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Subjects				
Any Post-Op complications? No	6			

Statistical analyses

No statistical analyses for this end point

Secondary: 30-Day post-operative mortality

End point title	30-Day post-operative mortality

End point description:

This is a single-arm study, therefore there are no statistical comparisons.
There were no deaths reported during the PRICKLE study, therefore this endpoint is not applicable.

End point type	Secondary

End point timeframe:

Deaths reported within 30 days following surgery

End point values	Abraxane & Gemcitabine treatment (Evaluable)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Subjects				
30-Day post-op death? No	6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	All Participants

Reporting group description: -

Serious adverse events	All Participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Febrile neutropenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Biliary tract infection			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All Participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
Vascular disorders			
Hot flashes			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Phlebitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chills			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Edema limbs			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	5		
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 9 (100.00%)		
occurrences (all)	41		
Fever			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	6		
Flu like symptoms			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	8		
General disorders - Other, rigor/shiver			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, coryzal symptoms			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Malaise			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			

Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	4		
Dyspnea			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	4		
Epistaxis			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	6		
Laryngeal inflammation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Productive cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Postnasal drip			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders - Other, mucositis nasal sores			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Sore throat			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Psychiatric disorders			

Depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 9 (66.67%)		
occurrences (all)	21		
Alkaline phosphatase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	17		
Aspartate aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	10		
Aspartate aminotransaminase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood bilirubin increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	8		
Investigations - Other, creactive protein increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Investigations - Other, leukocyte count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

Investigations - Other, leukocytes in urine			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Lymphocyte count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	8		
Neutrophil count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 9 (66.67%)		
occurrences (all)	16		
Pancreatic enzymes decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Platelet count decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	4		
Serum amylase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	4		
Weight loss			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
White blood cell decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	9		
Injury, poisoning and procedural complications			

Fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Nervous system disorders			
Dysesthesia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dysgeusia			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 9 (66.67%)		
occurrences (all)	12		
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	4		
Nervous system disorders - Other, migraine			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nervous system disorders - Other, vivid dreams			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Peripheral motor neuropathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Syncope			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Vasovagal reaction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	6		
Ear and labyrinth disorders			
Ear and labyrinth disorders - Other, dizziness and full sensation middle ear			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Ear pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Eye disorders			
Eye disorders - Other, cloudy eyes			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Watering eyes			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	8 / 9 (88.89%)			
occurrences (all)	15			
Bloating				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences (all)	2			
Constipation				
alternative assessment type: Non-systematic				
subjects affected / exposed	7 / 9 (77.78%)			
occurrences (all)	14			
Diarrhea				
alternative assessment type: Non-systematic				
subjects affected / exposed	9 / 9 (100.00%)			
occurrences (all)	22			
Dry mouth				
alternative assessment type: Non-systematic				
subjects affected / exposed	6 / 9 (66.67%)			
occurrences (all)	6			
Dyspepsia				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences (all)	2			
Fecal incontinence				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Flatulence				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Gastrointestinal disorders - Other, eructation				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			

Gastroesophageal reflux disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Gastrointestinal disorders - Other, reflux oesophagitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrointestinal disorders - Other, steatorrhea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Mucositis oral			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	6		
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 9 (88.89%)		
occurrences (all)	22		
Pancreatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Rectal hemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 9 (66.67%)		
occurrences (all)	27		
Hepatobiliary disorders			

Cholecystitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Hepatobiliary disorders - Other, biliary stent obstruction				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Skin and subcutaneous tissue disorders				
Alopecia				
alternative assessment type: Non-systematic				
subjects affected / exposed	8 / 9 (88.89%)			
occurrences (all)	16			
Dry skin				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Pruritus				
alternative assessment type: Non-systematic				
subjects affected / exposed	5 / 9 (55.56%)			
occurrences (all)	8			
Rash acneiform				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 9 (22.22%)			
occurrences (all)	4			
Purpura				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Rash maculo-papular				
alternative assessment type: Non-systematic				
subjects affected / exposed	7 / 9 (77.78%)			
occurrences (all)	18			
Skin and subcutaneous tissue disorders - Other, erythema				

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders - Other, rosacea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Urticaria			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Renal and urinary disorders			
Hematuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Proteinuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Renal and urinary disorders - Other, bacteriuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Renal and urinary disorders - Other, bilirubinuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Urinary frequency			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Urine discoloration			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Myalgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	4		
Infections and infestations			
Hepatitis viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Mucosal infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	4		
Soft tissue infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Upper respiratory infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Urinary tract infection			
alternative assessment type: Non-			

systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Vaginal infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Anorexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 9 (77.78%)		
occurrences (all)	23		
Hypoalbuminemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Metabolism and nutrition disorders - Other, glucose in urine			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2015	Safety & IMP updates following release of new Abraxane SmPC. Removal of SPARC analysis. Clarifications to procedures and assessment timing.
07 February 2017	Extension of the study by 12 months due to slower than expected recruitment.
30 June 2017	Protocol Reference Safety Information updated. Abraxane SmPC updates.

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.

N/A

Notes: