Clinical trial results:
A Phase II, randomised, open-label study of Gemcitabine/Carboplatin first-line chemotherapy in combination with or without the antisense oligonucleotide Apatorsen (OGX-427) in advanced squamous cell lung cancers.

EudraCT number	2014-000199-25
Trial protocol	GB
Global end of trial date	24 May 2018

Result version number	v1 (current)
This version publication date	29 June 2019
First version publication date	29 June 2019

Sponsor protocol code	009436

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02423590
WHO universal trial number (UTN)	-

Notes:

Sponsor organisation name	Queen Mary University of London
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Notes:

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:

Analysis stage	Final
Date of interim/final analysis	31 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2018
Global end of trial reached?	Yes
Global end of trial date	24 May 2018
Was the trial ended prematurely?	Yes

Notes:

Main objective of the trial:

To estimate the clinical benefit of gemcitabine/carboplatin plus Apatorsen (OGX-427) relative to gemcitabine /carboplatin alone, as measured by investigator-assessed progression-free survival (PFS).

Protection of trial subjects:

The study design aims to minimise potential risks. Eligibility criteria were selected to enhance the safety of patients in this trial and a number of exclusion criteria were specifically based on the known safety profiles of the study drug treatments. A dose modification strategy for management of toxicity and monitoring was in place for those risks deemed to be most likely or serious.

Background therapy:

All patients received gemcitabine and carboplatin, which were used within their licensed indications and were therefore regarded as non-investigational products. Commercial gemcitabine and carboplatin was sourced locally by the investigational sites in keeping with standard local practice. Commercial brands of gemcitabine and carboplatin were permitted for use.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	27 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Country: Number of subjects enrolled	United Kingdom: 86
Worldwide total number of subjects	86
EEA total number of subjects	86

Notes:

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	35
From 65 to 84 years	51
85 years and over	0

Recruitment details:

From June 2014 to December 2016 86 patients with advanced squamous cell lung cancer were recruited from 21 UK centres.

Screening details:

Patients with newly diagnosed cytologically or histologically confirmed Stage IIIB/IV squamous cell carcinoma, with no symptomatic CNS involvement or CNS involvement requiring steroids. ECOG perfomance status 0 - 2.
Adequate organ and bone marrow function, with no history of significant cardiovascular disease or polyneuropathy > Grade 2. .

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

Blinding implementation details:

Not applicable.

Are arms mutually exclusive?	Yes
	Gemcitabine/Carboplatin

Arm description:

Gemcitabine/carboplatin will be administered as standard 21-day treatment cycles according to normal clinical practice. Gemcitabine (1250 mg/m2) will be given by 30 minute intravenous infusions on Day 1 and Day 8 of each 21-day Cycle. Following the administration of gemcitabine on Day 1, carboplatin (AUC5) will be given by infusion over 30-60 minutes.

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

Dosage and administration details:

1250 mg/m2 given by 30 minute intravenous infusions on Day 1 and Day 8 of each 21-day Cycle.

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

Dosage and administration details:

Following the administration of gemcitabine on Day 1, carboplatin (AUC5) will be given by infusion over 30-60 minutes. AUC dose was calculated as per local guidelines. Sites could use the Calvert formula as a guide.

	Apatorsen plus gemcitabine/carboplatin

Arm description:

Gemcitabine/carboplatin was administered as standard 21-day treatment cycles according to normal clinical practice. Apatorsen (OGX-427) was administered prior to gemcitabine/carboplatin chemotherapy. Apatorsen (OGX-427) treatment began with a loading dose period prior to the initiation of chemotherapy. Patients received three loading doses of 400 mg by 2 hour intravenous infusions within a 9-day period (with at least 48 hours between start times of infusions and between the start of the last

infusion and the initiation of chemotherapy); following the loading dose period and upon initiation of the 21-day treatment cycles, 400mg Apatorsen (OGX-427) was given weekly by approximately 2 hour intravenous infusions. Gemcitabine was given by 30 minute intravenous infusions on Day 1 and Day 8 of each 21-day Cycle. Carboplatin was given by 30 to 60 minute infusion on Day 1 of each 21-day Cycle. Chemotherapy was initiated within 7 calendar days following completion of the loading dose period.

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1250 mg/m2 given by 30 minute intravenous infusions on Day 1 and Day 8 of each 21-day Cycle.

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

Dosage and administration details:

Following the administration of gemcitabine on Day 1, carboplatin (AUC5) will be given by infusion over 30-60 minutes. AUC dose was calculated as per local guidelines. Sites could use the Calvert formula as a guide.

Investigational medicinal product name	Apatorsen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Apatorsen (OGX-427) treatment began with a loading dose period prior to the initiation of chemotherapy. Patients received three loading doses of 400 mg by 2 hour intravenous infusions within a 9-day period (with at least 48 hours between start times of infusions and between the start of the last infusion and the initiation of chemotherapy); following the loading dose period and upon initiation of the 21-day treatment cycles, 400mg Apatorsen (OGX-427) was given weekly by approximately 2 hour intravenous infusions.

	Gemcitabine/Carboplatin	Apatorsen plus gemcitabine/carboplatin
Started	41	42
Completed	41	42

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 3 of the 86 randomised patients did not receive any treatment and were excluded from the analysis cohort.

Reporting group title	Gemcitabine/Carboplatin

Reporting group description:

Gemcitabine/carboplatin will be administered as standard 21-day treatment cycles according to normal clinical practice. Gemcitabine (1250 mg/m2) will be given by 30 minute intravenous infusions on Day 1 and Day 8 of each 21-day Cycle. Following the administration of gemcitabine on Day 1, carboplatin (AUC5) will be given by infusion over 30-60 minutes.

Reporting group title	Apatorsen plus gemcitabine/carboplatin

Reporting group description:

Gemcitabine/carboplatin was administered as standard 21-day treatment cycles according to normal clinical practice. Apatorsen (OGX-427) was administered prior to gemcitabine/carboplatin chemotherapy. Apatorsen (OGX-427) treatment began with a loading dose period prior to the initiation of chemotherapy. Patients received three loading doses of 400 mg by 2 hour intravenous infusions within a 9-day period (with at least 48 hours between start times of infusions and between the start of the last infusion and the initiation of chemotherapy); following the loading dose period and upon initiation of the 21-day treatment cycles, 400mg Apatorsen (OGX-427) was given weekly by approximately 2 hour intravenous infusions. Gemcitabine was given by 30 minute intravenous infusions on Day 1 and Day 8 of each 21-day Cycle. Carboplatin was given by 30 to 60 minute infusion on Day 1 of each 21-day Cycle. Chemotherapy was initiated within 7 calendar days following completion of the loading dose period.

	Gemcitabine/Carboplatin	Apatorsen plus gemcitabine/carboplatin	Total
Number of subjects	41	42	83
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0e	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23			

Units: Subjects			
IIIB	11	12	23
IV	30	30	60

Reporting group title	Gemcitabine/Carboplatin

Reporting group description:

Gemcitabine/carboplatin will be administered as standard 21-day treatment cycles according to normal clinical practice. Gemcitabine (1250 mg/m2) will be given by 30 minute intravenous infusions on Day 1 and Day 8 of each 21-day Cycle. Following the administration of gemcitabine on Day 1, carboplatin (AUC5) will be given by infusion over 30-60 minutes.

Reporting group title	Apatorsen plus gemcitabine/carboplatin

Reporting group description:

Gemcitabine/carboplatin was administered as standard 21-day treatment cycles according to normal clinical practice. Apatorsen (OGX-427) was administered prior to gemcitabine/carboplatin chemotherapy. Apatorsen (OGX-427) treatment began with a loading dose period prior to the initiation of chemotherapy. Patients received three loading doses of 400 mg by 2 hour intravenous infusions within a 9-day period (with at least 48 hours between start times of infusions and between the start of the last infusion and the initiation of chemotherapy); following the loading dose period and upon initiation of the 21-day treatment cycles, 400mg Apatorsen (OGX-427) was given weekly by approximately 2 hour intravenous infusions. Gemcitabine was given by 30 minute intravenous infusions on Day 1 and Day 8 of each 21-day Cycle. Carboplatin was given by 30 to 60 minute infusion on Day 1 of each 21-day Cycle. Chemotherapy was initiated within 7 calendar days following completion of the loading dose period.

End point title	Progression-free survival (PFS)

End point description:

End point type	Primary

End point timeframe:

PFS is defined as the time from date of randomisation to the date of first documented tumour progression or death from any cause, whichever occurs first.

	Gemcitabine/Carboplatin	Apatorsen plus gemcitabine/carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	42		
Units: months				
median (confidence interval 95%)	6.47 (5.32 to 7.33)	5.19 (3.25 to 5.82)		

	Log-rank test and Cox proportional hazards
Comparison groups	Gemcitabine/Carboplatin v Apatorsen plus gemcitabine/carboplatin

Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.174
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	2.27

End point title	Overall Survival (OS)

End point description:

End point type	Secondary

End point timeframe:

OS is defined as the time from date of randomisation to the date of death from any cause.

	Gemcitabine/Carboplatin	Apatorsen plus gemcitabine/carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	42		
Units: months				
median (confidence interval 95%)	12.98 (8.18 to 18.83)	9.10 (5.39 to 10.68)		

No statistical analyses for this end point

End point title	Objective response rate (ORR)

End point description:

End point type	Secondary

End point timeframe:

Patients with at least one confirmed complete response (CR) or partial response (PR) based on investigator assessment using RECIST v1.1.

	Gemcitabine/Carboplatin	Apatorsen plus gemcitabine/carboplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	42		
Units: Percentage				
number (confidence interval 95%)	21.95 (10.56 to 37.61)	19.05 (8.60 to 34.12)		

No statistical analyses for this end point

Timeframe for reporting adverse events:	
Adverse Events will be recorded from the day of written informed consent until 30 days after the last dose of study treatment. Prior to initiation of study medications, only SAEs caused by a protocol-mandated interventions will be reported.	
Assessment type	Systematic

Dictionary name	MedDRA
Dictionary version	17.1

Reporting group title	Gemcitabine/Carboplatin
Reporting group description:	
Gemcitabine/carboplatin will be administered as standard 21-day treatment cycles according to normal clinical practice. Gemcitabine (1250 mg/m2) will be given by 30 minute intravenous infusions on Day 1 and Day 8 of each 21-day Cycle. Following the administration of gemcitabine on Day 1, carboplatin (AUC5) will be given by infusion over 30-60 minutes.	
Reporting group title	Apatorsen plus gemcitabine/carboplatin
Reporting group description:	
Gemcitabine/carboplatin was administered as standard 21-day treatment cycles according to normal clinical practice. Apatorsen (OGX-427) was administered prior to gemcitabine/carboplatin chemotherapy. Apatorsen (OGX-427) treatment began with a loading dose period prior to the initiation of chemotherapy. Patients received three loading doses of 400 mg by 2 hour intravenous infusions within a 9-day period (with at least 48 hours between start times of infusions and between the start of the last infusion and the initiation of chemotherapy); following the loading dose period and upon initiation of the 21-day treatment cycles, 400mg Apatorsen (OGX-427) was given weekly by approximately 2 hour intravenous infusions. Gemcitabine was given by 30 minute intravenous infusions on Day 1 and Day 8 of each 21-day Cycle. Carboplatin was given by 30 to 60 minute infusion on Day 1 of each 21-day Cycle. Chemotherapy was initiated within 7 calendar days following completion of the loading dose period.	

	Gemcitabine/Carboplatin	Apatorsen plus gemcitabine/carboplatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 41 (41.46%)	30 / 42 (71.43%)	
number of deaths (all causes)	31	32	
number of deaths resulting from adverse events			
Investigations			
Pancytopenia			
subjects affected / exposed	1 / 41 (2.44%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 41 (2.44%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thrombocytopenia			
subjects affected / exposed	5 / 41 (12.20%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	6 / 7	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 41 (0.00%)	3 / 42 (7.14%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrilation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 41 (4.88%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 41 (7.32%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 41 (7.32%)	4 / 42 (9.52%)	
occurrences causally related to treatment / all	2 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 41 (0.00%)	6 / 42 (14.29%)	
occurrences causally related to treatment / all	0 / 0	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small bowel obstruction			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vomiting			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Unresponsiveness			

subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	4 / 41 (9.76%)	4 / 42 (9.52%)	
occurrences causally related to treatment / all	1 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 41 (4.88%)	4 / 42 (9.52%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia			
subjects affected / exposed	4 / 41 (9.76%)	6 / 42 (14.29%)	
occurrences causally related to treatment / all	1 / 4	1 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

	Gemcitabine/Carboplatin	Apatorsen plus gemcitabine/carboplatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 41 (100.00%)	42 / 42 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 41 (12.20%)	7 / 42 (16.67%)	
occurrences (all)	17	31	
Hypotension			
subjects affected / exposed	2 / 41 (4.88%)	4 / 42 (9.52%)	
occurrences (all)	2	5	
Thromboembolic event			
subjects affected / exposed	3 / 41 (7.32%)	3 / 42 (7.14%)	
occurrences (all)	3	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	31 / 41 (75.61%)	25 / 42 (59.52%)	
occurrences (all)	51	55	
Pain			
subjects affected / exposed	25 / 41 (60.98%)	18 / 42 (42.86%)	
occurrences (all)	33	38	
Fever			
subjects affected / exposed	7 / 41 (17.07%)	11 / 42 (26.19%)	
occurrences (all)	10	15	
Edema			
subjects affected / exposed	9 / 41 (21.95%)	4 / 42 (9.52%)	
occurrences (all)	9	6	
Chills			
subjects affected / exposed	2 / 41 (4.88%)	6 / 42 (14.29%)	
occurrences (all)	3	8	
Dysphonia			
subjects affected / exposed	2 / 41 (4.88%)	3 / 42 (7.14%)	
occurrences (all)	2	6	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	25 / 41 (60.98%)	29 / 42 (69.05%)	
occurrences (all)	41	61	
Cough			
subjects affected / exposed	23 / 41 (56.10%)	21 / 42 (50.00%)	
occurrences (all)	28	32	
Epistaxis			
subjects affected / exposed	7 / 41 (17.07%)	7 / 42 (16.67%)	
occurrences (all)	13	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 41 (17.07%)	6 / 42 (14.29%)	
occurrences (all)	7	8	
Investigations			
Thrombocytopenia			
subjects affected / exposed	14 / 41 (34.15%)	21 / 42 (50.00%)	
occurrences (all)	50	88	
Neutropenia			
subjects affected / exposed	9 / 41 (21.95%)	18 / 42 (42.86%)	
occurrences (all)	37	75	
Leucopenia			
subjects affected / exposed	5 / 41 (12.20%)	12 / 42 (28.57%)	
occurrences (all)	28	52	
Liver function test abnormal			
subjects affected / exposed	6 / 41 (14.63%)	7 / 42 (16.67%)	
occurrences (all)	14	36	
Hypocalcaemia			
subjects affected / exposed	4 / 41 (9.76%)	5 / 42 (11.90%)	
occurrences (all)	7	10	
Weight loss			
subjects affected / exposed	3 / 41 (7.32%)	6 / 42 (14.29%)	
occurrences (all)	4	8	
Lymphopenia			
subjects affected / exposed	3 / 41 (7.32%)	5 / 42 (11.90%)	
occurrences (all)	13	19	
Creatinine increased			

subjects affected / exposed	2 / 41 (4.88%)	4 / 42 (9.52%)	
occurrences (all)	6	11	
Hypokalaemia			
subjects affected / exposed	2 / 41 (4.88%)	3 / 42 (7.14%)	
occurrences (all)	2	5	
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	4 / 41 (9.76%)	3 / 42 (7.14%)	
occurrences (all)	5	3	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	3 / 41 (7.32%)	7 / 42 (16.67%)	
occurrences (all)	3	17	
Chest pain			
subjects affected / exposed	3 / 41 (7.32%)	4 / 42 (9.52%)	
occurrences (all)	3	5	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	7 / 41 (17.07%)	7 / 42 (16.67%)	
occurrences (all)	8	9	
Headache			
subjects affected / exposed	4 / 41 (9.76%)	7 / 42 (16.67%)	
occurrences (all)	5	20	
Dizziness			
subjects affected / exposed	3 / 41 (7.32%)	7 / 42 (16.67%)	
occurrences (all)	7	7	
Neuropathy			
subjects affected / exposed	3 / 41 (7.32%)	4 / 42 (9.52%)	
occurrences (all)	3	4	
Tremor			
subjects affected / exposed	2 / 41 (4.88%)	5 / 42 (11.90%)	
occurrences (all)	2	5	
Lethargy			
subjects affected / exposed	3 / 41 (7.32%)	3 / 42 (7.14%)	
occurrences (all)	5	3	
Paraesthesia			

subjects affected / exposed	3 / 41 (7.32%)	2 / 42 (4.76%)	
occurrences (all)	4	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 41 (51.22%)	24 / 42 (57.14%)	
occurrences (all)	92	145	
Localized edema			

subjects affected / exposed	1 / 41 (2.44%)	6 / 42 (14.29%)	
occurrences (all)	1	6	
Dry skin			
subjects affected / exposed	2 / 41 (4.88%)	3 / 42 (7.14%)	
occurrences (all)	2	3	
Hyperhidrosis			
subjects affected / exposed	1 / 41 (2.44%)	4 / 42 (9.52%)	
occurrences (all)	1	4	
Pruritus			
subjects affected / exposed	1 / 41 (2.44%)	4 / 42 (9.52%)	
occurrences (all)	3	7	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	12 / 41 (29.27%)	18 / 42 (42.86%)	
occurrences (all)	19	25	
Arthralgia			
subjects affected / exposed	3 / 41 (7.32%)	3 / 42 (7.14%)	
occurrences (all)	4	4	
Muscular weakness			
subjects affected / exposed	2 / 41 (4.88%)	3 / 42 (7.14%)	
occurrences (all)	2	4	
Infections and infestations			
Infection			
subjects affected / exposed	24 / 41 (58.54%)	26 / 42 (61.90%)	
occurrences (all)	43	52	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	14 / 41 (34.15%)	17 / 42 (40.48%)	
occurrences (all)	18	22	
Hypomagnesaemia			
subjects affected / exposed	6 / 41 (14.63%)	8 / 42 (19.05%)	
occurrences (all)	12	43	
Hyperglycaemia			
subjects affected / exposed	4 / 41 (9.76%)	3 / 42 (7.14%)	
occurrences (all)	4	10	
Hypertriglyceridaemia			

subjects affected / exposed	4 / 41 (9.76%)	3 / 42 (7.14%)	
occurrences (all)	8	5	
Hypercalcaemia			
subjects affected / exposed	4 / 41 (9.76%)	2 / 42 (4.76%)	
occurrences (all)	6	3	
Hypoalbuminaemia			
subjects affected / exposed	3 / 41 (7.32%)	3 / 42 (7.14%)	
occurrences (all)	4	4	

Were there any global substantial amendments to the protocol? Yes

23 May 2014	- Clarification of adverse reaction expectdness listed in the Protocol - List of prohibited medications amended to include live vaccines because they are not recommended in patients treated with gemcitabine. - Pharmacovigilance reporting clarification - Due to the gemcitabine cardiotoxic potential, ECG added at screening and when clinically indicated to the safety assessments. - As per SmPC requirements, neurological evaluation and an assessment of hearing must be performed on a regular basis in patients treated with carboplatin. - Contraception updates
18 August 2015	- Addition of exploratory objective to investigate any apatorsen benefit in a study subpopulation defined as having poor prognostic features.
15 March 2016	- Change to the dose of IMP from 600mg to 400mg following review of data provided by the IMP manufacturer on recently completed studies. - Expansion of inclusion criteria to better suit recent advances in treatment. Patients who have received previous first-line immunotherapy (without chemotherapy) were now eligible for the trial. Patients with cytological diagnosis of squamous cell cancer were also eligible following this amendment, previously only patients with a histological diagnosis were elligible. - Length of chemotherapy amended from ‘6 cycles’ to ‘4-6 cycles’ to reflect differences in local practice across all research sites.
21 February 2017	Reduction of sample size from 140 to 86 patients due to unavailability of IMP.

Notes:

Were there any global interruptions to the trial? Yes

05 January 2017	Halt to recruitment while preparing amendment to reduce protocol sample size.	-

Notes:

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

Not applicable.

Notes: