Clinical trial results:
GEMCITABINE COMBINED WITH THE mTOR INHIBITOR TEMSIROLIMUS (CCI-779) IN PATIENTS WITH INOPERABLE OR METASTATIC PANCREATIC CANCER

Summary

EudraCT number	2008-002791-10
Trial protocol	GR
Global end of trial date	27 May 2015

Results information

Result version number	v1 (current)
This version publication date	19 April 2019
First version publication date	19 April 2019

Trial information

Trial identification

Sponsor protocol code	HE 3/07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ANZCTR: ACTRN12611000643976

Notes:

Sponsors

Sponsor organisation name	Hellenic Cooperative Oncology Group
Sponsor organisation address	Hatzikonstandi 18, Athens, Greece, 11524
Public contact	Hellenic Cooperative Oncology Group, Hellenic Cooperative Oncology Group, hecogoff@otenet.gr
Scientific contact	Hellenic Cooperative Oncology Group, Hellenic Cooperative Oncology Group, hecogoff@otenet.gr

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	05 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is:
1. Determine the maximum tolerated dose and recommended phase II dose of temsirolimus and gemcitabine in patients with pancreatic cancer.
2. To estimate the progression free survival in patients treated with the temsirolimus+gemcitabine combination.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial. A copy of the IEC/IRB approval was received by the sponsor before recruitment of subjects into the study and all subjects provided written informed consent before undergoing any study-related procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 May 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 85
Worldwide total number of subjects	85
EEA total number of subjects	85

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)	52
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in the study from 19 May 2009 until 8 October 2014 from 8 sites in Greece.

Pre-assignment

Screening details:

Patients signed the informed consent form and were screened for eligibility before entering the study

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I

Arm description:

Chemotherapy naive patients with inoperable or metastatic pancreatic carcinoma were enrolled to the study in 6 dose levels in order to determine the maximum tolerated dose and recommended Phase II dose of temsirolimus and gemcitabine.

Arm type	Experimental
Investigational medicinal product name	TORISEL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Level 1: 10mg
Level 2: 15mg
Level 3: 20mg
Level 4: 25mg
Level 5: 20mg
Level 6: 25mg

Arm title	Phase II

Arm description:

Dose level 6 of gemcitabine 1000mg/m2 and temsirolimus 25mg was the recomended dose for the Phase II study in patients with inoperable or metastatic pancreatic cancer

Arm type	Experimental
Investigational medicinal product name	TORISEL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Torisel 25mg was the recomended dose for the Phase II study

Number of subjects in period 1	Phase I	Phase II
Started	30	55
Completed	3	4
Not completed	27	51
Clinical progression	2	-
Adverse event, serious fatal	-	4
Consent withdrawn by subject	-	5
Physician decision	-	1
Disease progression	16	31
Adverse event, non-fatal	3	8
Non-starter	1	-
Death	1	2
More than one month elapsed	1	-
Performance status lower than 50	1	-
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Phase I
Reporting group description:	
Chemotherapy naive patients with inoperable or metastatic pancreatic carcinoma were enrolled to the study in 6 dose levels in order to determine the maximum tolerated dose and recommended Phase II dose of temsirolimus and gemcitabine.	
Reporting group title	Phase II
Reporting group description:	
Dose level 6 of gemcitabine 1000mg/m2 and temsirolimus 25mg was the recomended dose for the Phase II study in patients with inoperable or metastatic pancreatic cancer	

Reporting group values	Phase I	Phase II	Total
Number of subjects	30	55	85
Age categorical			
Units: Subjects			
Adults (18-64 years)	19	33	52
From 65-84 years	11	22	33
85 years and over	0	0	0
Age continuous			
Units: years			
median	62.4	62.1	
full range (min-max)	42.2 to 81.3	38.7 to 77.8	-
Gender categorical			
Units: Subjects			
Female	14	23	37
Male	16	32	48

End points

End points reporting groups

Reporting group title	Phase I

Reporting group description:

Chemotherapy naive patients with inoperable or metastatic pancreatic carcinoma were enrolled to the study in 6 dose levels in order to determine the maximum tolerated dose and recommended Phase II dose of temsirolimus and gemcitabine.

Reporting group title	Phase II

Reporting group description:

Dose level 6 of gemcitabine 1000mg/m2 and temsirolimus 25mg was the recomended dose for the Phase II study in patients with inoperable or metastatic pancreatic cancer

Primary: Maximum Tolerated Dose of Gemcitabine (G) and Temsirolimus (T)

End point title	Maximum Tolerated Dose of Gemcitabine (G) and Temsirolimus (T)[1][2]

End point description:

In the Phase I part of the study, 30 patients were enrolled, at least 3 subjects at each dose level in order to determine the recommended dose for the Phase II part of the study.

End point type	Primary

End point timeframe:

From study initiation until the determination of the maximum tolerated dose.

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: Gemcitabine doses per dose level are described for patients enrolled in the Phase I part of the study.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The determination of the maximum tolerated dose of Gemcitabine and Temsirolimus was the primary endpoint of the Phase I part of the study. The number of patients evaluable for DLT per dose level is described for patients enrolled in the Phase I part of the study.

End point values	Phase I			
Subject group type	Reporting group			
Number of subjects analysed	30[3]			
Units: number of patients evaluable for DLT				
Dose Level 1 G (800mg/m2),T (10 mg)	7			
Dose Level 2 G (800mg/m2), T(15mg)	3			
Dose Level 3 G(800mg/m2),T(20 mg)	6			
Dose Level 4 G(800mg/m2),T(25 mg)	3			
Dose Level 5 G (1000 mg/m2),T(20 mg)	3			
Dose Level 6 G(1000 mg/m2),T(25 mg)	3			

Notes:

[3] - In the first dose level one patient did not start treatment and one was ineligible.

Statistical analyses

No statistical analyses for this end point

Primary: 6-month Progression Free Survival

End point title	6-month Progression Free Survival[4][5]

End point description:

Progression- Free Survival (PFS) was calculated from the date of study entry to the date of first documented progression, death or last contact.

End point type	Primary

End point timeframe:

tumor assessments were performed in cycles 2,4 and 7

Notes:

[4] - 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: Since this was a single arm Phase I/II trial and all patients were treated with Gemcitabine and Temsirolimus, no comparisons between different treatment arms were performed. The percentage of patients surviving 6 months since study entry has been provided for the patients included in the Phase II part of the study.
[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The 6-month progression free survival rate was the primary endpoint of the Phase II part of the study. The percentage of Phase II patients surviving 6 months since study entry is described.

End point values	Phase II			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: percentage of surviving patients				
number (not applicable)	30.9			

Attachments (see zip file)	Kaplan-Meier for PFS/KM_PFS_29112018.tiff

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life benefits

End point title	Quality of life benefits[6]

End point description:

Quality of life was assessed using the EUROQOL 5D Questionnaire. The descriptive system consists of 5 dimensions including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The single summary EQ-5D Index was calculated using the European value set.

End point type	Secondary

End point timeframe:

Quality of life questionnaires were completed on screening-baseline, on cycles 4, 7 and 6 months after completion of treatment

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The Quality of Life assessment was a secondary endpoint of the Phase II part of the trial and therefore measures of central tendency and dispersion of the calculated EQ-5D Index are provided for Phase II patients that completed the EQ-5D questionnaire at baseline and at the last treatment cycle.

End point values	Phase II			
Subject group type	Reporting group			
Number of subjects analysed	55[7]			
Units: EQ-5D Index				
arithmetic mean (standard deviation)				
Baseline	0.67 (± 0.21)			
Last treatment cycle	0.65 (± 0.26)			

Notes:

[7] - 51 patients (92.7%) completed the EQ-5D questionnaire at baseline and 30 at the last treatment cycle

Attachments (see zip file)	Histogram of the difference of EQ-5D Index/EQ5D_Difference.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival[8]

End point description:

End point type	Secondary

End point timeframe:

overall survival was measured from the date of patient's study entry to the date of death or last contact.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Overall Survival was a secondary endpoint of the Phase II part of the trial. Therefore, the median overall survival (in months) with the corresponding 95% confidence intervals are provided for the 55 patients included in the Phase II part of the study.

End point values	Phase II			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: months				
median (confidence interval 95%)	4.95 (3.54 to 6.85)			

Attachments (see zip file)	Kaplan-Meier for Overall Survival/KM_OS_29112018.tiff

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events and serious adverse events of temsirolimus combination and gemcitabine

End point title	Adverse events and serious adverse events of temsirolimus combination and gemcitabine

End point description:

Assessment of the nature, incidence and severity of adverse events and serious adverse events of the

combination of temsirolmus and gemcitabine.

End point type	Secondary

End point timeframe:

Adverse events and serious adverse events of all participants were recorded and assessed upon signature of the inform consent until 30 days after the last administration of study treatment.

End point values	Phase I	Phase II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[9]	55		
Units: number of patients				
Any Adverse Event	29	53		
Adverse Events grade ≥3	28	47		
Adverse Events grade ≥4	8	25		
Fatal Adverse Events	1	5		
Serious Adverse Events	14	31		

Notes:

[9] - One patient never started treatment and was therefore excluded from the safety population.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Upon signature of the informed consent form until 30 days after the last administration of the investigational medicinal product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups

Reporting group title	Phase I

Reporting group description:

chemotherapy naive patients with inoperable or metastatic pancreatic carcinoma were enrolled to the study in 6 dose levels in order to determine the maximum tolerated dose and recomended Phase II dose of temsirolimus and gemcitabine

Reporting group title	Phase II

Reporting group description:

dose level 6 of gemcitabine 1000mg/m2 and temsirolimus 25mg was the recomended dose for the Phase II study in patients with inoperable or metastatic pancreatic cancer

Serious adverse events	Phase I	Phase II	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 29 (48.28%)	31 / 55 (56.36%)	
number of deaths (all causes)	1	54	
number of deaths resulting from adverse events	1	5	
Investigations			
bilirubin total increased			
subjects affected / exposed	2 / 29 (6.90%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			

subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 29 (3.45%)	6 / 55 (10.91%)	
occurrences causally related to treatment / all	1 / 1	6 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Thrombosis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hematoma			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chest pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
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	1 / 29 (3.45%)	5 / 55 (9.09%)	
occurrences causally related to treatment / all	1 / 1	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
tumour progression	Additional description: clinical tumour progression		
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
multiple organ failure			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
fatigue			
subjects affected / exposed	1 / 29 (3.45%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
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	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 29 (3.45%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	2 / 29 (6.90%)	6 / 55 (10.91%)	
occurrences causally related to treatment / all	2 / 2	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
hemorrhage upper gastrointestinal NOS			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (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	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 29 (3.45%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
stent obstruction			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
obstruction of the bile duct			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
obstruction of the biliary tract			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
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			
Pneumonitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratory infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (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			
Pneumonia	Additional description: pneumonia infection which was caused due to Klebsiella		
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sepsis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infection			
subjects affected / exposed	2 / 29 (6.90%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
infection bladder			

subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 29 (0.00%)	4 / 55 (7.27%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bacteraemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 29 (0.00%)	3 / 55 (5.45%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
infection with grade 3 lymphopenia			
alternative dictionary used: CTCAE 3			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Opportunistic infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
stent infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
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: 0 %

Non-serious adverse events	Phase I	Phase II	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 29 (96.55%)	52 / 55 (94.55%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 29 (3.45%)	1 / 55 (1.82%)	
occurrences (all)	2	1	
Flushing			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Phlebitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Embolism			
subjects affected / exposed	1 / 29 (3.45%)	3 / 55 (5.45%)	
occurrences (all)	1	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	15 / 29 (51.72%)	19 / 55 (34.55%)	
occurrences (all)	25	21	
fever			
subjects affected / exposed	8 / 29 (27.59%)	12 / 55 (21.82%)	
occurrences (all)	11	28	
Chills			
subjects affected / exposed	2 / 29 (6.90%)	1 / 55 (1.82%)	
occurrences (all)	2	2	
flu like symptoms			
alternative dictionary used: ctcae 4.03			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
other-paraneoplastic fever			
alternative dictionary used: ctcae 4.03			

subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
other-cold			
alternative dictionary used: ctcae 4.03			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Oedema mouth			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Inflammation	Additional description: inflammation of toe		
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
oedema limb			
alternative dictionary used: ctcae 4.03			
subjects affected / exposed	3 / 29 (10.34%)	3 / 55 (5.45%)	
occurrences (all)	3	3	
other-oedema head and neck			
alternative dictionary used: ctcae 4.03			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Immune system disorders			
allergic reaction			
alternative dictionary used: ctcae 4.03			
subjects affected / exposed	0 / 29 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
other-allergic in food factor			
alternative dictionary used: ctcae 4.03			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
vagina pain			
alternative dictionary used: ctcae 3			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal			

disorders			
Epistaxis			
subjects affected / exposed	4 / 29 (13.79%)	4 / 55 (7.27%)	
occurrences (all)	4	6	
other-pharynx pain			
alternative dictionary used: CTC AE 3			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 29 (3.45%)	2 / 55 (3.64%)	
occurrences (all)	2	2	
Dyspnoea			
subjects affected / exposed	2 / 29 (6.90%)	0 / 55 (0.00%)	
occurrences (all)	2	0	
Hiccups			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
voice alteration			
alternative dictionary used: ctcae 4.03			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Pneumonitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 55 (1.82%)	
occurrences (all)	1	1	
Mood altered			
subjects affected / exposed	0 / 29 (0.00%)	5 / 55 (9.09%)	
occurrences (all)	0	5	
Hallucination	Additional description: occasionally		
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Investigations			

White blood cell decreased			
subjects affected / exposed	25 / 29 (86.21%)	36 / 55 (65.45%)	
occurrences (all)	98	130	
Lymphocyte count decreased			
subjects affected / exposed	1 / 29 (3.45%)	2 / 55 (3.64%)	
occurrences (all)	5	2	
Neutrophil count decreased			
subjects affected / exposed	23 / 29 (79.31%)	33 / 55 (60.00%)	
occurrences (all)	77	120	
Platelet count decreased			
subjects affected / exposed	16 / 29 (55.17%)	32 / 55 (58.18%)	
occurrences (all)	47	74	
Weight decreased			
subjects affected / exposed	3 / 29 (10.34%)	1 / 55 (1.82%)	
occurrences (all)	3	1	
Alanine aminotransferase increased			
subjects affected / exposed	23 / 29 (79.31%)	31 / 55 (56.36%)	
occurrences (all)	57	52	
Aspartate aminotransferase increased			
subjects affected / exposed	19 / 29 (65.52%)	29 / 55 (52.73%)	
occurrences (all)	55	56	
Alkaline Phosphatase Increased	Additional description: ALP serum increased		
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	8 / 29 (27.59%)	19 / 55 (34.55%)	
occurrences (all)	11	23	
Blood bilirubin increased			
subjects affected / exposed	4 / 29 (13.79%)	14 / 55 (25.45%)	
occurrences (all)	8	18	
Hypercholesterolaemia			
subjects affected / exposed	3 / 29 (10.34%)	4 / 55 (7.27%)	
occurrences (all)	3	4	
creatinine increased	Additional description: serum creatinine increased		
alternative dictionary used: CTCAE 4.03			
subjects affected / exposed	4 / 29 (13.79%)	4 / 55 (7.27%)	
occurrences (all)	5	7	

Gamma-glutamyltransferase increased			
subjects affected / exposed	14 / 29 (48.28%)	25 / 55 (45.45%)	
occurrences (all)	14	27	
Injury, poisoning and procedural complications			
Vascular access complication			
subjects affected / exposed	1 / 29 (3.45%)	2 / 55 (3.64%)	
occurrences (all)	1	2	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Atrial fibrillation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 55 (1.82%)	
occurrences (all)	1	1	
Nightmare			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	3	0	
Somnolence			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	

Tremor			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	4 / 29 (13.79%)	0 / 55 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 29 (58.62%)	33 / 55 (60.00%)	
occurrences (all)	30	52	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 29 (10.34%)	7 / 55 (12.73%)	
occurrences (all)	3	9	
Diarrhoea			
subjects affected / exposed	6 / 29 (20.69%)	13 / 55 (23.64%)	
occurrences (all)	7	16	
Dry mouth			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Cheilitis			
subjects affected / exposed	0 / 29 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	1 / 29 (3.45%)	2 / 55 (3.64%)	
occurrences (all)	1	2	
Stomatitis			
subjects affected / exposed	5 / 29 (17.24%)	12 / 55 (21.82%)	
occurrences (all)	5	14	
Nausea			
subjects affected / exposed	7 / 29 (24.14%)	9 / 55 (16.36%)	
occurrences (all)	12	12	
Vomiting			

subjects affected / exposed	4 / 29 (13.79%)	7 / 55 (12.73%)	
occurrences (all)	9	11	
Abdominal pain			
subjects affected / exposed	12 / 29 (41.38%)	10 / 55 (18.18%)	
occurrences (all)	26	16	
Haemorrhoids			
subjects affected / exposed	4 / 29 (13.79%)	0 / 55 (0.00%)	
occurrences (all)	4	0	
Dysphagia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	0 / 29 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
Haemorrhage	Additional description: lower GI NOS		
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	4	0	
Rash			
subjects affected / exposed	8 / 29 (27.59%)	13 / 55 (23.64%)	
occurrences (all)	11	16	
Pruritus			
subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)	
occurrences (all)	2	2	
nail changes			
alternative dictionary used: ctcae 3			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Renal and urinary disorders			
urinary frequency			
alternative dictionary used: ctcae 4.03			
subjects affected / exposed	1 / 29 (3.45%)	1 / 55 (1.82%)	
occurrences (all)	1	1	

Urinary retention			
subjects affected / exposed	0 / 29 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
Haematuria	Additional description: microscopic		
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Endocrine disorders			
Glucose tolerance impaired			
subjects affected / exposed	0 / 29 (0.00%)	4 / 55 (7.27%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
muscle weakness			
alternative dictionary used: ctcae 4.03			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	5 / 29 (17.24%)	5 / 55 (9.09%)	
occurrences (all)	9	5	
Infections and infestations			
other-dermatology herpes			
alternative dictionary used: ctcae 3			
subjects affected / exposed	0 / 29 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
Catheter site infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 29 (3.45%)	4 / 55 (7.27%)	
occurrences (all)	1	4	
Viral infection			
subjects affected / exposed	2 / 29 (6.90%)	0 / 55 (0.00%)	
occurrences (all)	2	0	
Fungal infection			
subjects affected / exposed	3 / 29 (10.34%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 29 (3.45%)	2 / 55 (3.64%)	
occurrences (all)	1	2	
Nail infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
other-herpetic mucositis			
alternative dictionary used: ctcae 3			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	2	
Candida infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
anorexia			
subjects affected / exposed	13 / 29 (44.83%)	11 / 55 (20.00%)	
occurrences (all)	17	11	
Hyperglycaemia			
subjects affected / exposed	18 / 29 (62.07%)	21 / 55 (38.18%)	
occurrences (all)	46	34	
Hyperkalaemia			
subjects affected / exposed	6 / 29 (20.69%)	4 / 55 (7.27%)	
occurrences (all)	11	5	
Hypermagnesaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Hypernatraemia			
subjects affected / exposed	1 / 29 (3.45%)	3 / 55 (5.45%)	
occurrences (all)	1	6	
Hypertriglyceridaemia			
subjects affected / exposed	4 / 29 (13.79%)	6 / 55 (10.91%)	
occurrences (all)	4	8	
Hyperuricaemia			
subjects affected / exposed	1 / 29 (3.45%)	3 / 55 (5.45%)	
occurrences (all)	1	6	
Hypoalbuminaemia			

subjects affected / exposed	14 / 29 (48.28%)	13 / 55 (23.64%)	
occurrences (all)	22	20	
Hypocalcaemia			
subjects affected / exposed	5 / 29 (17.24%)	13 / 55 (23.64%)	
occurrences (all)	7	21	
Hypoglycaemia			
subjects affected / exposed	1 / 29 (3.45%)	2 / 55 (3.64%)	
occurrences (all)	1	2	
Hypokalaemia			
subjects affected / exposed	8 / 29 (27.59%)	7 / 55 (12.73%)	
occurrences (all)	16	11	
Hyponatraemia			
subjects affected / exposed	7 / 29 (24.14%)	15 / 55 (27.27%)	
occurrences (all)	15	28	
Hypomagnesaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Hypophosphataemia			
subjects affected / exposed	1 / 29 (3.45%)	2 / 55 (3.64%)	
occurrences (all)	1	2	
other-LDH			
alternative dictionary used: ctcae 4.03			
subjects affected / exposed	4 / 29 (13.79%)	1 / 55 (1.82%)	
occurrences (all)	10	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2012	changes in reporting requirements of serious adverse events

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported