Clinical trial results:
An International, Multi-Center, Double-Blind, Randomized, Phase III Trial of 90Y-Clivatuzumab Tetraxetan plus Low-Dose Gemcitabine Versus Placebo plus Low-Dose Gemcitabine in Patients with Metastatic (Stage IV) Pancreatic Adenocarcinoma Who Received at Least Two Prior Treatments (PANCRIT-1)

Summary

EudraCT number	2013-004516-21
Trial protocol	AT ES FR PL BE
Global end of trial date	14 March 2016

Results information

Result version number	v1 (current)
This version publication date	13 April 2018
First version publication date	13 April 2018

Trial information

Trial identification

Sponsor protocol code	IMMU-107-04

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Immunomedics, Inc.
Sponsor organisation address	300 The American Road, Morris Plains, United States, New Jersey 07950
Public contact	Diane Whiteley, Senior Director Regulatory Affairs, Immunomedics, Inc., 1 973-605-8200, dwhiteley@immunomedics.com
Scientific contact	Diane Whiteley, Senior Director Regulatory Affairs, Immunomedics, Inc., 1 973-605-8200, dwhiteley@immunomedics.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 March 2016
Global end of trial reached?	Yes
Global end of trial date	14 March 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that patients with metastatic (Stage IV) pancreatic adenocarcinoma previously treated with at least 2 systemic chemotherapy regimens had increased overall survival (OS) if they received fractionated radioimmunotherapy with 90Y-clivatuzumab tetraxetan plus low-dose gemcitabine compared to those receiving placebo plus low-dose gemcitabine.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.
To maximize therapeutic benefit, patients could have stopped treatment in the event of unacceptable toxicity, but otherwise received as many multiple cycles or doses as possible, following dose reduction guidelines to reduce, delay, or hold the study drugs in the event of hematological or other toxicities.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 December 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Spain: 81
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	United States: 196
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Israel: 4
Worldwide total number of subjects	333
EEA total number of subjects	125

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)	171
From 65 to 84 years	160
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening period was up to 4 weeks.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

90Y-clivatuzumab Tetraxetan + Gemcitabine

Arm type	Experimental
Investigational medicinal product name	90Y-clivatuzumab Tetraxetan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Three once-weekly doses of 6.5 mCi/m2 (240.5 MBq/m2) 90Y-clivatuzumab tetraxetan were administered on cycle weeks 2, 3 and 4 (cycle days 6, 13, and 20), and no study agent was administered on cycle weeks 5, 6 or 7. Each dose of 6.5 mCi/m2 (240.5 MBq/m2) 90Y-clivatuzumab tetraxetan was intravenously administered by slow push over 5 minutes or less.

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

Dosage and administration details:

Four once-weekly doses of 200 mg/m2 gemcitabine were administered on cycle weeks 1, 2, 3 and 4 (cycle days 1, 8, 15 and 22), and no study agent was administered on cycle weeks 5, 6 or 7. Each dose of gemcitabine was given intravenously over 30 minutes.

Arm title	Arm B

Arm description:

Placebo + Gemcitabine

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

Dosage and administration details:

Three once-weekly doses of placebo control were administered on cycle weeks 2, 3 and 4 (cycle days 6,

13, and 20), and no study agent was administered on cycle weeks 5, 6 or 7. Each dose of placebo control was intravenously administered by slow push over 5 minutes or less.

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

Dosage and administration details:

Four once-weekly doses of 200 mg/m2 gemcitabine were administered on cycle weeks 1, 2, 3 and 4 (cycle days 1, 8, 15 and 22), and no study agent was administered on cycle weeks 5, 6 or 7. Each dose of gemcitabine was given intravenously over 30 minutes.

Number of subjects in period 1	Arm A	Arm B
Started	221	112
Completed	0	0
Not completed	221	112
Adverse event, serious fatal	42	13
Consent withdrawn by subject	21	9
Adverse event, non-fatal	11	4
Progressive disease per imaging	72	48
Other	14	4
Not eligible prior to treatment	8	4
Progressive disease clinical	26	15
Sponsor decision	27	15

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description: 90Y-clivatuzumab Tetraxetan + Gemcitabine	
Reporting group title	Arm B
Reporting group description: Placebo + Gemcitabine	

Reporting group values	Arm A	Arm B	Total
Number of subjects	221	112	333
Age categorical Units: Subjects			
Adults (18-64 years)	112	59	171
From 65-84 years	108	52	160
85 years and over	1	1	2
Gender categorical Units: Subjects			
Female	92	46	138
Male	129	66	195

End points

End points reporting groups	
Reporting group title	Arm A
Reporting group description:	
90Y-clivatuzumab Tetraxetan + Gemcitabine	
Reporting group title	Arm B
Reporting group description:	
Placebo + Gemcitabine	

Primary: Overall Survival	
End point title	Overall Survival
End point description:	
End point type	Primary
End point timeframe:	
Intent-to-Treat Population, cut-off date 17 April 2016.	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	112		
Units: Months				
number (confidence interval 95%)	2.96 (2.53 to 3.71)	2.92 (2.60 to 3.25)		

Statistical analyses

Statistical analysis title	Treatment comparison (90Y versus placebo)
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4362 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.27

Notes:
[1] - P-value (1-sided) was obtained using unstratified log rank test.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE reporting continued for 30 days after either the last dose of study treatment or until the patient initiated alternative antineoplastic therapy not permitted during this study. Thereafter, AE reporting was limited to events judged study drug-related.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	90Y-clivatuzumab Tetraxetan + Gemcitabine
Reporting group description: -	
Reporting group title	Placebo + Gemcitabine

Reporting group description: -

Serious adverse events	90Y-clivatuzumab Tetraxetan + Gemcitabine	Placebo + Gemcitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 191 (28.80%)	19 / 97 (19.59%)	
number of deaths (all causes)	11	0	
number of deaths resulting from adverse events	11	0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 191 (0.52%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			

subjects affected / exposed	1 / 191 (0.52%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Local swelling			
subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 191 (1.05%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 191 (2.62%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			

subjects affected / exposed	1 / 191 (0.52%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 191 (0.52%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	8 / 191 (4.19%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	10 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic ulcer			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Embolic stroke			
subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 191 (1.05%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 191 (2.62%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	5 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	3 / 191 (1.57%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 191 (1.05%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 191 (1.57%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Nausea			
subjects affected / exposed	2 / 191 (1.05%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			

subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic mass			

subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 191 (1.05%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Enterococcal bacteraemia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex encephalitis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 191 (0.52%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal infection			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			

subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 191 (1.05%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 191 (1.05%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 191 (1.05%)	3 / 97 (3.09%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Septic shock			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 191 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	90Y-clivatuzumab Tetraxetan + Gemcitabine	Placebo + Gemcitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	185 / 191 (96.86%)	87 / 97 (89.69%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 191 (1.57%)	3 / 97 (3.09%)	
occurrences (all)	4	4	
Hypotension			
subjects affected / exposed	12 / 191 (6.28%)	4 / 97 (4.12%)	
occurrences (all)	12	5	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	40 / 191 (20.94%)	13 / 97 (13.40%)	
occurrences (all)	71	16	
Chills			
subjects affected / exposed	12 / 191 (6.28%)	3 / 97 (3.09%)	
occurrences (all)	18	3	
Fatigue			
subjects affected / exposed	67 / 191 (35.08%)	33 / 97 (34.02%)	
occurrences (all)	91	44	
Oedema peripheral			
subjects affected / exposed	26 / 191 (13.61%)	4 / 97 (4.12%)	
occurrences (all)	35	4	
Pain			
subjects affected / exposed	2 / 191 (1.05%)	3 / 97 (3.09%)	
occurrences (all)	2	3	
Pyrexia			
subjects affected / exposed	42 / 191 (21.99%)	13 / 97 (13.40%)	
occurrences (all)	55	20	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 191 (6.81%)	3 / 97 (3.09%)	
occurrences (all)	13	3	

Dyspnoea			
subjects affected / exposed	24 / 191 (12.57%)	10 / 97 (10.31%)	
occurrences (all)	28	15	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 191 (3.14%)	5 / 97 (5.15%)	
occurrences (all)	6	7	
Confusional state			
subjects affected / exposed	6 / 191 (3.14%)	1 / 97 (1.03%)	
occurrences (all)	6	1	
Insomnia			
subjects affected / exposed	9 / 191 (4.71%)	4 / 97 (4.12%)	
occurrences (all)	11	5	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 191 (3.66%)	4 / 97 (4.12%)	
occurrences (all)	11	6	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 191 (1.57%)	4 / 97 (4.12%)	
occurrences (all)	6	6	
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 191 (3.14%)	0 / 97 (0.00%)	
occurrences (all)	8	0	
Blood bilirubin increased			
subjects affected / exposed	12 / 191 (6.28%)	4 / 97 (4.12%)	
occurrences (all)	14	6	
Lymphocyte count decreased			
subjects affected / exposed	11 / 191 (5.76%)	3 / 97 (3.09%)	
occurrences (all)	22	3	
Neutrophil count decreased			
subjects affected / exposed	35 / 191 (18.32%)	14 / 97 (14.43%)	
occurrences (all)	67	32	
Neutrophil count increased			
subjects affected / exposed	1 / 191 (0.52%)	4 / 97 (4.12%)	
occurrences (all)	1	4	
Platelet count decreased			

subjects affected / exposed	112 / 191 (58.64%)	22 / 97 (22.68%)	
occurrences (all)	356	37	
Weight decreased			
subjects affected / exposed	12 / 191 (6.28%)	7 / 97 (7.22%)	
occurrences (all)	14	7	
White blood cell count decreased			
subjects affected / exposed	23 / 191 (12.04%)	5 / 97 (5.15%)	
occurrences (all)	40	18	
White blood cell count increased			
subjects affected / exposed	4 / 191 (2.09%)	4 / 97 (4.12%)	
occurrences (all)	4	4	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 191 (1.57%)	3 / 97 (3.09%)	
occurrences (all)	3	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 191 (5.76%)	2 / 97 (2.06%)	
occurrences (all)	16	2	
Dysgeusia			
subjects affected / exposed	7 / 191 (3.66%)	4 / 97 (4.12%)	
occurrences (all)	7	4	
Headache			
subjects affected / exposed	7 / 191 (3.66%)	1 / 97 (1.03%)	
occurrences (all)	7	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	73 / 191 (38.22%)	23 / 97 (23.71%)	
occurrences (all)	139	39	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	11 / 191 (5.76%)	3 / 97 (3.09%)	
occurrences (all)	13	3	
Abdominal distension			
subjects affected / exposed	13 / 191 (6.81%)	2 / 97 (2.06%)	
occurrences (all)	14	2	
Abdominal pain			

subjects affected / exposed	53 / 191 (27.75%)	21 / 97 (21.65%)	
occurrences (all)	74	23	
Abdominal pain upper			
subjects affected / exposed	15 / 191 (7.85%)	5 / 97 (5.15%)	
occurrences (all)	19	5	
Ascites			
subjects affected / exposed	24 / 191 (12.57%)	11 / 97 (11.34%)	
occurrences (all)	27	12	
Constipation			
subjects affected / exposed	28 / 191 (14.66%)	13 / 97 (13.40%)	
occurrences (all)	35	14	
Diarrhoea			
subjects affected / exposed	26 / 191 (13.61%)	14 / 97 (14.43%)	
occurrences (all)	30	20	
Dry mouth			
subjects affected / exposed	6 / 191 (3.14%)	4 / 97 (4.12%)	
occurrences (all)	6	4	
Dyspepsia			
subjects affected / exposed	8 / 191 (4.19%)	1 / 97 (1.03%)	
occurrences (all)	8	1	
Eructation			
subjects affected / exposed	0 / 191 (0.00%)	3 / 97 (3.09%)	
occurrences (all)	0	3	
Nausea			
subjects affected / exposed	52 / 191 (27.23%)	23 / 97 (23.71%)	
occurrences (all)	73	26	
Stomatitis			
subjects affected / exposed	8 / 191 (4.19%)	3 / 97 (3.09%)	
occurrences (all)	8	3	
Vomiting			
subjects affected / exposed	49 / 191 (25.65%)	13 / 97 (13.40%)	
occurrences (all)	63	14	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	7 / 191 (3.66%)	1 / 97 (1.03%)	
occurrences (all)	7	1	

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 191 (0.00%)	3 / 97 (3.09%)	
occurrences (all)	0	3	
Night sweats			
subjects affected / exposed	2 / 191 (1.05%)	3 / 97 (3.09%)	
occurrences (all)	2	3	
Pruritus			
subjects affected / exposed	6 / 191 (3.14%)	3 / 97 (3.09%)	
occurrences (all)	6	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 191 (0.52%)	6 / 97 (6.19%)	
occurrences (all)	1	7	
Back pain			
subjects affected / exposed	21 / 191 (10.99%)	9 / 97 (9.28%)	
occurrences (all)	27	11	
Muscular weakness			
subjects affected / exposed	6 / 191 (3.14%)	1 / 97 (1.03%)	
occurrences (all)	8	1	
Musculoskeletal chest pain			
subjects affected / exposed	6 / 191 (3.14%)	1 / 97 (1.03%)	
occurrences (all)	7	1	
Musculoskeletal pain			
subjects affected / exposed	10 / 191 (5.24%)	3 / 97 (3.09%)	
occurrences (all)	11	3	
Myalgia			
subjects affected / exposed	6 / 191 (3.14%)	5 / 97 (5.15%)	
occurrences (all)	6	5	
Neck pain			
subjects affected / exposed	2 / 191 (1.05%)	3 / 97 (3.09%)	
occurrences (all)	2	3	
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 191 (3.14%)	2 / 97 (2.06%)	
occurrences (all)	6	2	

Urinary tract infection			
subjects affected / exposed	6 / 191 (3.14%)	3 / 97 (3.09%)	
occurrences (all)	7	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	49 / 191 (25.65%)	20 / 97 (20.62%)	
occurrences (all)	62	23	
Dehydration			
subjects affected / exposed	11 / 191 (5.76%)	4 / 97 (4.12%)	
occurrences (all)	13	5	
Hyperglycaemia			
subjects affected / exposed	8 / 191 (4.19%)	2 / 97 (2.06%)	
occurrences (all)	12	2	
Hypokalaemia			
subjects affected / exposed	6 / 191 (3.14%)	5 / 97 (5.15%)	
occurrences (all)	7	5	
Hyponatraemia			
subjects affected / exposed	6 / 191 (3.14%)	1 / 97 (1.03%)	
occurrences (all)	7	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2014	- Edited inclusion criteria to clarify that qualifying patients should have received at least 2 prior systemic cytotoxic chemotherapy regimens for treatment of unresectable locally advanced or metastatic disease. Clarified that 1 of the prior systemic cytotoxic chemotherapy regimens must have contained gemcitabine and that patients must have met a list of specified criteria regarding the gemcitabine regimen; - Updated dose reduction/delay/discontinuation rules in the event of hematological toxicities, infusion reactions, or other toxicities of various grades, including clarification for reduced dosing, missed doses, coordination of gemcitabine dosing, and gemcitabine toxicity; - Clarified that 2 samples would be collected during the first treatment cycle and a third serum sample for pharmacokinetic assessments was to be collected at baseline for the determination of antibody levels; - Added additional language to describe the preparation and assay of radiolabeled 90Y-clivatuzumab tetraxetan at prescribed doses that exceeded 8 mL in a single 10-mL syringe. These doses would be prepared by using two 10-mL syringes, each adjusted to a final volume of 8 mL, which could be separately assayed and the activities combined; and - Clarified that adverse event (AE) reporting would continue for 30 days (not >30 days) after either the last dose of study drug or until the patient initiated alternative antineoplastic therapy not permitted during this study. Thereafter, AE reporting was to be limited to study drug-related events.
26 October 2015	- Clarified that during Weeks 2, 3, and 4 of each treatment cycle, the weekly complete blood count should have been obtained prior to the 90Y-clivatuzumab tetraxetan or placebo control dose in order to evaluate for cytopenias that may have required the dose to be reduced, delayed, or discontinued; - Required Karnofsky Performance Status (KPS), patient weight, and the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire evaluations on the fourth week of each treatment cycle in order to obtain additional data for analysis of treatment benefit; - Clarified that randomization was to be stratified on the basis of the number of prior treatments for either unresectable locally advanced or metastatic disease; - Removed wording regarding serum samples collected for determination of PAM4-reactive mucin, since this exploratory analysis was to no longer be performed by the Sponsor; and - Removed inadvertent reference to urinalysis which was not required in this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 March 2016	The study was stopped due to futility based on the Data and Safety Monitoring Board recommendation.	-

Notes:

Limitations and caveats

None reported