Clinical trial results:
LICC: L-BLP25 in Patients with Colorectal Carcinoma after curative resection of hepatic metastases – a randomized, placebo-controlled, multicenter, multinational, double blinded phase II trial

Summary

EudraCT number	2011-000218-20
Trial protocol	DE AT BE
Global end of trial date	24 January 2018

Results information

Result version number	v1 (current)
This version publication date	06 March 2019
First version publication date	06 March 2019
Summary attachment (see zip file)	LICC_Synopse_EudraCT_20190124 (LICC_Synopse_EudraCT_20190124.pdf)

Trial information

Trial identification

Sponsor protocol code	LICC01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01462513
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mainz University Medical Center
Sponsor organisation address	Langenbeckstraße 1, Mainz, Germany, 55131
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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	31 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 January 2018
Global end of trial reached?	Yes
Global end of trial date	24 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was the comparative evaluation of recurrence-free survival time and three year overall survival between the treatment groups cyclophosphamide + tecemotide (L-BLP25) versus saline + placebo.

Protection of trial subjects:

The trial was performed in accordance with the ethical principles laid down in the Declaration of Helsinki and are consistent with Good Clinical Practice. The informed consent form (ICF) of patients was obtained prior to study participation in accordance with a) §40 I 3 No. Lit., b) II 1 AMG and § 40 I 3 No. 3 Lit and c) IIa 1&2 AMG. Nature, objective and consequences of the study, possible benefits and disadvantages, risks and the study procedure were explained to each patient orally and in writing. The patients were informed that, by signing the ICF, they permitted authorized representatives of the sponsor and the regulatory authorities to access study-related personal data without violating the confidentiality of the patient. Patients were informed that their consent to access their data might not be revoked. Each patient was given enough time to read and discuss the ICF with the investigator prior to giving written consent. Before entry to the study and prior to the conduct of any study-related procedure, consent was recorded by means of the patient's dated signature. Each patient was given a copy of the information sheet and his/her signed consent form. Only eligible patients were included into this study. Clinical site monitoring was conducted to ensure that the rights of the subjects were protected. Safety assessments consisted of regular monitoring and recording of (serious) adverse events until 30 days after the end of treatment and regular monitoring of hematology, blood chemistry, vital signs and physical condition during the whole treatment phase, with special attention paid to signs and symptoms that might have indicated an autoimmune disorder. Dose adjustments were not permitted for patients who did not tolerate dosing as per protocol. The trial blind might have been broken in case of an emergency. Epinephrine, antihistamine and hydrocortisone were available in the event of an anaphylactic reaction.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Germany: 119
Worldwide total number of subjects	121
EEA total number of subjects	121

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)	80
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with metastatic colorectal carcinoma, who had undergone complete resection of their primary tumor & recent resection of their liver metastases (R0 or R1) were recruited within 8 weeks after resection with curative intent. Out of 25 centers initiated in GER & AT (BE was dropped) 22 recruited patients after intial EC approval on 27.09.2011.

Pre-assignment

Screening details:

Eligible patients were randomized via IVRS to treatment with cyclophosphamide + tecemotide versus saline + placebo (2:1) following the receipt of informed consent, completion of all baseline evaluations, and determination of patient eligibility. The randomization to a treatment arm was performed in a stratified manner by resection status R0 v R1.

Pre-assignment period milestones

Number of subjects started	133[1]
Intermediate milestone: Number of subjects	Randomization: 121
Number of subjects completed	121

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Patients who did not meet entry criteria: 9
Reason: Number of subjects	Duplicate randomization: 1
Reason: Number of subjects	Patients who declined participation: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of 133 patients screened, 9 patients did not meet the selection criteria for study entry and 2 patients declined participation. One patient was randomized twice. The first randomization of this patient was excluded from analysis. A total of 121 patients were randomized into the study, 79 (65.3%) patients to the tecemotide arm and 42 (34.7%) patients to the placebo arm.

Period 1

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

Blinding implementation details:

Medication for primary- and maintenance treatments with tecemotide or placebo were packaged identically. Traceability of content was ensured by the combination of kit- batch- and medication-number. Cyclophosphamide or saline infusions were prepared by an unblinded pharmacist; to prevent unblinding of investigators a volume of saline solution corresponding to the calculated volume of cyclophosphamide solution was withdrawn from the infusion bag, so that both infusions had the same volume.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - tecemotide + cyclophosphamide (ITT population)

Arm description:

Subjects represented in Arm A received a single iv infusion of 300 mg/m2 (to a maximum of 600 mg) cyclophosphamide 3 days prior to the first tecemotide treatment. Subjects then received 8 consecutive subcutaneous treatments with 930 µg tecemotide at weeks 1, 2, 3, 4, 5, 6, 7 and 8 followed by maintenance treatment (930 µg tecemotide) at 6-week intervals commencing at week 14, until either recurrence was documented or a treatment period of a total of 2 years was reached. Subjects were discontinued from the study treatment upon recurrence documented by imaging.

Arm type	Investigational
Investigational medicinal product name	Tecemotide
Investigational medicinal product code	L-BLP25
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The IMP (tecemotide) was supplied as a lyophilized powder and stored at 2-8°C. Prior to administration, the powder was reconstituted with sterile 0.9% sodium chloride solution. One vial of the IMP provided drug material for the preparation of a 0.50 mL injection aliquot. The total treatment dose was prepared from four vials of the product. Per each treatment, four 0.50 mL injections were administered to the patient by subcutaneous application at four different anatomical sites.

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

Dosage and administration details:

A single iv infusion of 300 mg/m2 of cyclophosphamide was administered within seven days of randomization and three days (72 hours ± 8 hours) prior to first tecemotide treatment. Cyclophosphamide was dissolved in a 50 mL 0.9 % saline solution prior to administration. A low dose of cyclophosphamide was given with the intention of overcoming tolerance and enhancing any effect of immunotherapy.

Arm title	Arm B - placebo + saline - (ITT population)

Arm description:

Subjects represented in Arm B received a single iv infusion of a volume of saline solution matching the volume of cyclophosphamide solution that would have been given to the subject if he/she were allocated to the verum arm. This was given 3 days prior to the first placebo application. Subjects then received 8 consecutive subcutaneous treatments with placebo at weeks 1, 2, 3, 4, 5, 6, 7 and 8 followed by maintenance treatment at 6-week intervals commencing at week 14, until either recurrence was documented or a treatment period of a total of 2 years was reached. Subjects were discontinued from the study treatment upon recurrence documented by imaging.

Arm type	Control Arm
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

The placebo was formulated to provide the same carrier lipid matrix as tecemotide, but without the adjuvant (monophosphoryl lipid A) and BLP25 lipopeptide. Therefore, it should not elicit a MUC1-specific immune response or have an effect on RFS or OS time. A single iv infusion of 0.9% sodium chloride, in the same calculated volume as used for cyclophosphamide dose in the investigational arm, was given to subjects in the control arm within 7 days of randomization and three days (72 hours ± 8 hours) before administering first placebo treatment.

Number of subjects in period 1	Arm A - tecemotide + cyclophosphamide (ITT population)	Arm B - placebo + saline - (ITT population)
Started	79	42
Completed	65	40
Not completed	14	2
Other reason	2	-
Lost to follow-up	12	2

Baseline characteristics

Reporting groups

Reporting group title	Arm A - tecemotide + cyclophosphamide (ITT population)

Reporting group description:

Subjects represented in Arm A received a single iv infusion of 300 mg/m2 (to a maximum of 600 mg) cyclophosphamide 3 days prior to the first tecemotide treatment. Subjects then received 8 consecutive subcutaneous treatments with 930 µg tecemotide at weeks 1, 2, 3, 4, 5, 6, 7 and 8 followed by maintenance treatment (930 µg tecemotide) at 6-week intervals commencing at week 14, until either recurrence was documented or a treatment period of a total of 2 years was reached. Subjects were discontinued from the study treatment upon recurrence documented by imaging.

Reporting group title	Arm B - placebo + saline - (ITT population)

Reporting group description:

Subjects represented in Arm B received a single iv infusion of a volume of saline solution matching the volume of cyclophosphamide solution that would have been given to the subject if he/she were allocated to the verum arm. This was given 3 days prior to the first placebo application. Subjects then received 8 consecutive subcutaneous treatments with placebo at weeks 1, 2, 3, 4, 5, 6, 7 and 8 followed by maintenance treatment at 6-week intervals commencing at week 14, until either recurrence was documented or a treatment period of a total of 2 years was reached. Subjects were discontinued from the study treatment upon recurrence documented by imaging.

Reporting group values	Arm A - tecemotide + cyclophosphamide (ITT population)	Arm B - placebo + saline - (ITT population)	Total
Number of subjects	79	42	121
Age categorical			
Units: Subjects			
Adults (18-64 years)	50	30	80
From 65-84 years	29	12	41
Age continuous			
Units: years			
median	60	58.5	
full range (min-max)	24 to 84	30 to 85	-
Gender categorical			
Units: Subjects			
Female	30	15	45
Male	49	27	76
ECOG Performance Status			
Units: Subjects			
ECOG 0	61	24	85
ECOG 1	18	18	36
MUC1 positive staining			
Mucin 1 (MUC1) is an overexpressed glycoprotein in colorectal carcinoma tissue. The expression status was described as an indicator of poor prognosis and a predictor of RFS and OS. The cancer vaccine, tecemotide, composed of liposomes carrying the antigen BLP25 lipopeptide and the adjuvant monophosphoryl lipid A, was expected to trigger an enhanced immune response targeting tumor cells with MUC1 expression. Therefore subgroups of MUC1 expression were formed according to expression levels to elucidate a potential connection between MUC1 expression state and survival outcome.			
Units: Subjects			
Low	11	5	16
Moderate	30	18	48
Strong	22	10	32
Not evaluable	16	8	24

Missing	0	1	1
Smoking status Units: Subjects			
Never	37	28	65
Ex	36	9	45
Current	6	5	11
Alcohol consumption Units: Subjects			
Not regularly	58	35	93
Regularly	16	5	21
Daily	5	2	7
TNM: T at first diagnosis Units: Subjects			
T1	4	0	4
T2	7	5	12
T3	52	30	82
T4	13	6	19
TX	3	1	4
TNM: N at first diagnosis Units: Subjects			
N0	21	12	33
N1	34	16	50
N2	19	12	31
NX	5	2	7
TNM: M at first diagnosis Units: Subjects			
M0	37	8	45
M1	37	28	65
MX	5	6	11
Tumor grading at first diagnosis Units: Subjects			
G1	1	1	2
G2	61	30	91
G3	11	9	20
G4	0	1	1
GX	6	1	7
Resection status Units: Subjects			
R0	69	38	107
R1	9	4	13
R2	1	0	1
Site of Tumor Units: Subjects			
Colon, exact site not known	9	3	12
Colon ascending	7	5	12
Colon descending	25	18	43
Colon multiple sites	1	0	1
Colon transversal, exact site not known	2	1	3
Colon transversal, proximal	1	1	2
Rectum	34	14	48

Number of resected metastases Units: Subjects			
Number of resections: < 5	70	34	104
Number of resections: 5-10	8	6	14
Number of resections: > 10	1	2	3
BMI at screening Units: kg/m²			
median	25.3	24.9	
full range (min-max)	18.3 to 49.6	19.4 to 57.7	-
Time since first diagnosis Units: months			
median	20.0	12.6	
full range (min-max)	1.4 to 121.3	0.9 to 73.6	-

End points

End points reporting groups

Reporting group title	Arm A - tecemotide + cyclophosphamide (ITT population)

Reporting group description:

Subjects represented in Arm A received a single iv infusion of 300 mg/m2 (to a maximum of 600 mg) cyclophosphamide 3 days prior to the first tecemotide treatment. Subjects then received 8 consecutive subcutaneous treatments with 930 µg tecemotide at weeks 1, 2, 3, 4, 5, 6, 7 and 8 followed by maintenance treatment (930 µg tecemotide) at 6-week intervals commencing at week 14, until either recurrence was documented or a treatment period of a total of 2 years was reached. Subjects were discontinued from the study treatment upon recurrence documented by imaging.

Reporting group title	Arm B - placebo + saline - (ITT population)

Reporting group description:

Subjects represented in Arm B received a single iv infusion of a volume of saline solution matching the volume of cyclophosphamide solution that would have been given to the subject if he/she were allocated to the verum arm. This was given 3 days prior to the first placebo application. Subjects then received 8 consecutive subcutaneous treatments with placebo at weeks 1, 2, 3, 4, 5, 6, 7 and 8 followed by maintenance treatment at 6-week intervals commencing at week 14, until either recurrence was documented or a treatment period of a total of 2 years was reached. Subjects were discontinued from the study treatment upon recurrence documented by imaging.

Primary: Recurrence Free Survival (RFS)

End point title	Recurrence Free Survival (RFS)

End point description:

The RFS was defined as time from date of randomisation until date of recurrence of disease or date of death if no recurrence was documented. RFS was determined by imaging.

End point type	Primary

End point timeframe:

The timeframe for RFS analysis was from date of randomisation until recurrence or death, whichever occured first. Observation of RFS was limited to 36 months from date of randomisation.

End point values	Arm A - tecemotide + cyclophosphamide (ITT population)	Arm B - placebo + saline - (ITT population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[1]	42[2]		
Units: months				
median (confidence interval 80%)	6.1 (5.9 to 8.8)	11.4 (8.6 to 19.8)		

Notes:

[1] - 18 patients from arm A were censored for analysis.

[2] - 14 patients from arm B were censored for analysis.

Attachments (see zip file)	Kaplan-Meier Plot for RFS (ITT)/Kaplan-Meier Plot for

Statistical analyses

Statistical analysis title	Kaplan-Meier Method

Statistical analysis description:

Kaplan-Meier method was used for analysis of RFS. Patients were censored if they were declared lost to follow-up, if they withdrew from the study before recurrence or death and if no event was observed during follow-up for recurrence. Recurrence-free time for patients not determined to have a progression of their disease were to be censored as of the date of the last evaluation of recurrence status.

Comparison groups	Arm A - tecemotide + cyclophosphamide (ITT population) v Arm B - placebo + saline - (ITT population)
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1754 [3]
Method	stratified Logrank-Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.338
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.925
upper limit	1.97

Notes:

[3] - A stratified log-rank test with stratification factor resection status was conducted for the difference in RFS distribution.

Primary: 3-year Overall Survival (OS)

End point title	3-year Overall Survival (OS)

End point description:

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

End point type	Primary

End point timeframe:

The timeframe for OS analysis was from date of randomisation to death or at least up to clinical data cutoff date (31-JAN-2018).

End point values	Arm A - tecemotide + cyclophosphamide (ITT population)	Arm B - placebo + saline - (ITT population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[4]	42[5]		
Units: Percent				
number (not applicable)	69.1	79.1		

Notes:

[4] - 49 patients from arm A were censored for analysis.

[5] - 30 patients from arm B were censored for analysis.

Attachments (see zip file)	Kaplan-Meier Plot for OS (ITT)/Kaplan-Meier Plot for Overall

Statistical analyses

Statistical analysis title	Kaplan-Meier Method

Statistical analysis description:

Kaplan-Meier method was used for analysis of OS. Patients lost to follow-up and patients who withdrew from the study were censored at the time of last contact or time of withdrawal, respectively. Data of patients alive at their individual end of study were censored at date of last contact or, if this was not available, at date of last visit.

Comparison groups	Arm A - tecemotide + cyclophosphamide (ITT population) v Arm B - placebo + saline - (ITT population)
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2141
Method	stratified Logrank-Test

Secondary: 3-year RFS of MUC1 positive cancer patients

End point title	3-year RFS of MUC1 positive cancer patients

End point description:

The 3-year RFS rate of MUC1 positive cancer patients was defined as time from date of randomisation until date of recurrence of disease or date of death if no recurrence was documented and was analysed using Kaplan-Meier-Method.

End point type	Secondary

End point timeframe:

The timeframe for 3-year RFS analysis was from date of randomisation until recurrence or death, whichever occured first. Observation of RFS was limited to 36 months from date of randomisation.

End point values	Arm A - tecemotide + cyclophosphamide (ITT population)	Arm B - placebo + saline - (ITT population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[6]	42[7]		
Units: Percent				
number (not applicable)				
low MUC1 staining	36.4	0.0		
moderate MUC1 staining	14.6	20.8		
strong MUC1 staining	22.7	44.4		

Notes:

[6] - Censored patients Arm A for low (n=4), moderate (n=6) and strong (n=5) MUC1 staining.

[7] - Censored patients Arm B for low (n=0), moderate (n=4) and strong (n=6) MUC1 staining.

Attachments (see zip file)	Kaplan-Meier Plot for 3-year RFS stratified byMUC1/Kaplan-

Statistical analyses

No statistical analyses for this end point

Secondary: 3-year OS of MUC1 positive cancer patients

End point title	3-year OS of MUC1 positive cancer patients

End point description:

3-year OS was analysed using Kaplan-Meier-Method.

End point type	Secondary

End point timeframe:

OS time was computed as time from date of randomisation up to clinical data cutoff date (31-JAN-2018).

End point values	Arm A - tecemotide + cyclophosphamide (ITT population)	Arm B - placebo + saline - (ITT population)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[8]	42[9]		
Units: Percent				
number (not applicable)				
low MUC1 staining	66.3	60.0		
moderate MUC1 staining,	78.7	83.0		
strong MUC1 staining,	74.7	85.7		

Notes:

[8] - Censored patients Arm A for low (n=8), moderate (n=22) and strong (n=14) MUC1 staining.

[9] - Censored patients Arm B for low (n=3), moderate (n=14) and strong (n=7) MUC1 staining.

Attachments (see zip file)	Kaplan-Meier Plot for 3-year OS stratified by MUC1/Kaplan-

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The (S)AE reporting period for safety surveillance began when the subject was enrolled in the trial and continued through the trial, until End of Treatment visit. Any SAE supected to be related to treatment must have been reported, whenever it occured.

Adverse event reporting additional description:

At each trial visit, the subject was queried on condition changes. During the reporting period of the trial any unfavorable changes in the subject's condition were recorded as (S)AEs. Any AE that occured during the course of the clinical trial and was suspected to be related to the IMP and all (S)AEs have been monitored and followed up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Arm A - tecemotide + cyclophosphamide - Safety Population

Reporting group description:

Safety endpoints were assessed for all patients who were treated with at least iv cyclophosphamide and for whom follow-up safety data was documented (= Safety Population). For patients who withdrew from the trial or were lost to follow-up, AEs were recorded and analysed until the time of withdrawal or time of last contact. The numbers provided are treatment emergent events.

Reporting group title	Arm B - placebo + saline - Safety population

Reporting group description:

Safety endpoints were assessed for all patients who were treated with at least iv saline and for whom follow-up safety data was documented (= Safety Population). For patients who withdrew from the trial or were lost to follow-up, AEs were recorded and analysed until the time of withdrawal or time of last contact. The numbers provided are treatment emergent events.

Serious adverse events	Arm A - tecemotide + cyclophosphamide - Safety Population	Arm B - placebo + saline - Safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 79 (29.11%)	14 / 42 (33.33%)	
number of deaths (all causes)	30	12	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to abdominal wall			
subjects affected / exposed	0 / 79 (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	
Metastases to lung			

subjects affected / exposed	2 / 79 (2.53%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 79 (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	
Vascular disorders			
Arterial occlusive disease			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 79 (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	
Surgical and medical procedures			
Enterostomy			
subjects affected / exposed	0 / 79 (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	
Pregnancy, puerperium and perinatal conditions			
Postpartum haemorrhage			
subjects affected / exposed	0 / 79 (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	
General disorders and administration site conditions			
General physical health deterioration			

subjects affected / exposed	2 / 79 (2.53%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	0 / 79 (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	
Injection site induration			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated hernia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 79 (2.53%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchopleural fistula			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pickwickian syndrome			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 79 (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	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 79 (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 bilirubin increased			
subjects affected / exposed	0 / 79 (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	
International normalised ratio increased			
subjects affected / exposed	0 / 79 (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	
Injury, poisoning and procedural complications			
Fracture			

subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 79 (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	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 79 (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	
Postoperative delirium			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 79 (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	
Spinal compression fracture			
subjects affected / exposed	0 / 79 (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	
Cardiac disorders			
Right ventricular failure			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 79 (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	
Syncope			

subjects affected / exposed	0 / 79 (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	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic haematoma			
subjects affected / exposed	0 / 79 (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	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 79 (1.27%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 79 (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	

Gastritis			
subjects affected / exposed	1 / 79 (1.27%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	3 / 79 (3.80%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 79 (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	
Large intestine perforation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 79 (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	
Rectal haemorrhage			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	0 / 79 (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	
Subileus			

subjects affected / exposed	0 / 79 (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	
Umbilical hernia			
subjects affected / exposed	0 / 79 (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	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (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 / 79 (1.27%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	2 / 79 (2.53%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Kidney congestion			
subjects affected / exposed	0 / 79 (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	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (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			
Bronchitis			
subjects affected / exposed	2 / 79 (2.53%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (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 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 79 (1.27%)	0 / 42 (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: 5 %

Non-serious adverse events	Arm A - tecemotide + cyclophosphamide - Safety Population	Arm B - placebo + saline - Safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 79 (87.34%)	40 / 42 (95.24%)	
Vascular disorders			

Hypertension			
subjects affected / exposed	7 / 79 (8.86%)	4 / 42 (9.52%)	
occurrences (all)	7	4	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 79 (8.86%)	2 / 42 (4.76%)	
occurrences (all)	10	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 79 (3.80%)	3 / 42 (7.14%)	
occurrences (all)	3	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 79 (24.05%)	8 / 42 (19.05%)	
occurrences (all)	27	11	
Injection site erythema			
subjects affected / exposed	7 / 79 (8.86%)	1 / 42 (2.38%)	
occurrences (all)	17	2	
Injection site reaction			
subjects affected / exposed	6 / 79 (7.59%)	3 / 42 (7.14%)	
occurrences (all)	25	11	
Injection site swelling			
subjects affected / exposed	4 / 79 (5.06%)	0 / 42 (0.00%)	
occurrences (all)	4	0	
Oedema peripheral			
subjects affected / exposed	3 / 79 (3.80%)	4 / 42 (9.52%)	
occurrences (all)	4	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 79 (5.06%)	3 / 42 (7.14%)	
occurrences (all)	6	4	
Abdominal pain upper			
subjects affected / exposed	4 / 79 (5.06%)	2 / 42 (4.76%)	
occurrences (all)	4	2	
Diarrhoea			

subjects affected / exposed	15 / 79 (18.99%)	7 / 42 (16.67%)	
occurrences (all)	21	10	
Flatulence			
subjects affected / exposed	2 / 79 (2.53%)	6 / 42 (14.29%)	
occurrences (all)	2	6	
Nausea			
subjects affected / exposed	24 / 79 (30.38%)	8 / 42 (19.05%)	
occurrences (all)	28	8	
Vomiting			
subjects affected / exposed	3 / 79 (3.80%)	6 / 42 (14.29%)	
occurrences (all)	3	6	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 79 (6.33%)	3 / 42 (7.14%)	
occurrences (all)	5	3	
Erythema			
subjects affected / exposed	4 / 79 (5.06%)	2 / 42 (4.76%)	
occurrences (all)	8	2	
Pruritus			
subjects affected / exposed	3 / 79 (3.80%)	6 / 42 (14.29%)	
occurrences (all)	3	11	
Rash			
subjects affected / exposed	3 / 79 (3.80%)	3 / 42 (7.14%)	
occurrences (all)	4	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 79 (1.27%)	3 / 42 (7.14%)	
occurrences (all)	1	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 79 (6.33%)	5 / 42 (11.90%)	
occurrences (all)	6	7	
Back pain			
subjects affected / exposed	6 / 79 (7.59%)	2 / 42 (4.76%)	
occurrences (all)	7	5	
Pain in extremity			

subjects affected / exposed	5 / 79 (6.33%)	1 / 42 (2.38%)	
occurrences (all)	5	1	
Infections and infestations			
Sinusitis			
subjects affected / exposed	1 / 79 (1.27%)	3 / 42 (7.14%)	
occurrences (all)	1	3	
Urinary tract infection			
subjects affected / exposed	1 / 79 (1.27%)	3 / 42 (7.14%)	
occurrences (all)	1	4	
Viral upper respiratory tract infection			
subjects affected / exposed	14 / 79 (17.72%)	4 / 42 (9.52%)	
occurrences (all)	14	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2011	The following changes were implemented through the first amendment of the protocol (V.2.0 to V.3.0): The frequency of pregnancy testing was increased to monthly for Austrian female subjects as requested by the austrian ethics comittee.
26 September 2012	The following changes were implemented through the second amendment of the protocol (V.3.0 to V.4.0): The inclusion criteria were adapted and the time between resection and randomization was extended to give patients more time to recover from operation and participate in adequate rehabilitation measures.
03 March 2015	The following changes were implemented through the third amendment of the protocol (V.4.0 to V.5.0): • The treatment period was shortened from 3 to 2 years as the development of tecemotide for Non Small Cell Lung Cancer was discontinued by Merck KGaA. • Study endpoints were changed. As per original study protocol, the primary endpoint was RFS; 3-year OS rate was added as a co-primary endpoint. • Sample size calculation was changed. The sample size was reduced from 159 to 120 patients due to slow recruitment and issues regarding supply of medication. • The reporting period for AEs was changed. AEs suspected to be related to the investigational product had to be recorded until the end of the treatment evaluation (12 weeks after last treatment). SAEs suspected to be related to the investigational product had to be reported during whole follow up period. • The recruitment period was extended from Q3 2013 to Q4 2014. • Handling of medication after reconstitution was amended. Update according to handling instruction v2.0. • The inclusion criterion regarding coagulation was changed. Anticoagulated patients were allowed in the trial. • The end of follow-up period was changed to 3 years after randomization of last patient. • The number and total volume of blood sampling for translational program was changed. • The definition of the evaluation of RFS time was changed. Individual treatment time was limited until recurrence or a maximum of 2 years. • The current investigational status was changed. Clinical development of tecemotide has been discontinued.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The trial served as a signal-finding study; statistically analyses have to be considered as fully explorative; high fraction of censored patients and a low number of patients in subgroup analysis limiting the explanatory power of Kaplan-Meier curves.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22494623