



Clinical trial results:

A multi-center, randomized, open-label, mechanism of action trial on the biological effects of the therapeutic cancer vaccine Stimuvax® (L-BLP25) in rectal cancer subjects undergoing neoadjuvant chemoradiotherapy.

Summary

EudraCT number	2011-000847-25
Trial protocol	BE PT DE NL AT
Global end of trial date	12 June 2014

Results information

Result version number	v1 (current)
This version publication date	13 June 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	EMR 63325-013
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01507103
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.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	12 June 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this mechanistic study is to determine the impact of L-BLP25 vaccine on the mucinous glycoprotein 1 - (MUC1) specific immune response in patients with newly diagnosed rectal cancer who are eligible for neoadjuvant therapy.

L-BLP25 is designed to induce an immune response that may lead to immune rejection of tumor tissues that aberrantly express MUC1 antigen. MUC1 is highly expressed in all colorectal cancers and since the adaptive immune system plays a role in the prognosis of rectal cancer, it is reasonable to speculate that the vaccination with L BLP25 might boost the tumor-specific response and increase the number of TILs.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 18
Country: Number of subjects enrolled	Portugal: 23
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 43
Worldwide total number of subjects	124
EEA total number of subjects	124

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)	81
From 65 to 84 years	42
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First/last subject (informed consent): Feb 2012/Dec 2013. Study completion date: Jun 2014.

Pre-assignment

Screening details:

Enrolled: 140 screened for eligibility; 16 subjects were not randomized due to non-fulfillment of inclusion or exclusion criteria and 124 subjects were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA

Arm description:

Single dose of cyclophosphamide 300 milligram per square meter [mg/m^2] to a maximum of 600 milligram [mg]) was administered intravenously, 3 days prior to the start of vaccination, followed by weekly subcutaneous vaccinations with tecemotide (L-BLP25) (actual delivered dose was 806 microgram [mcg]) administered concomitantly with chemotherapy for 8 weeks, followed by a 9th subcutaneous vaccination 7 to 11 days prior to surgery.

Arm type	Experimental
Investigational medicinal product name	Chemoradiotherapy (Radiotherapy+Captecitabine or - Fluorouracil)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radiopharmaceutical precursor, solution
Routes of administration	Not mentioned , Oral use

Dosage and administration details:

Radiotherapy of 45-52 grays (Gy) was applied 5 times per week, over a minimum period of 5 weeks. Capecitabine at a dose of $825 \text{ mg}/\text{m}^2$, twice daily or equivalent dose of 5-fluorouracil (5-FU) was administered orally, starting at the first day of radiotherapy and given 5 to 7 days per week during the time of radiotherapy.

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

Dosage and administration details:

Subjects received 8 consecutive weekly subcutaneous vaccinations with 806 mcg of tecemotide at Weeks 1, 2, 3, 4, 5, 6, 7 and 8, concomitantly with the chemoradiotherapy, followed by a 9th subcutaneous injection 7 to 11 days prior to surgery.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

A single intravenous infusion of $300 \text{ mg}/\text{m}^2$ (to a maximum 600 mg) of CPA was given 3 days before the first tecemotide (L-BLP25) administration.

Arm title	Chemoradiotherapy+Tecemotide (L-BLP25)
Arm description: Weekly subcutaneous vaccinations with tecemotide (L-BLP25) (actual delivered dose was 806 mcg) administered concomitantly with chemotherapy for 8 weeks, followed by a 9th subcutaneous vaccination 7 to 11 days prior to surgery.	
Arm type	Experimental
Investigational medicinal product name	Tecemotide (L-BLP25)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received 8 consecutive weekly subcutaneous vaccinations with 806 mcg of tecemotide (L-BLP25) at Weeks 1, 2, 3, 4, 5, 6, 7 and 8, concomitantly with the chemoradiotherapy, followed by a 9th subcutaneous injection 7 to 11 days prior to surgery.

Investigational medicinal product name	Chemoradiotherapy (Radiotherapy+Captecitabine or - Fluorouracil)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radiopharmaceutical precursor, solution
Routes of administration	Not mentioned

Dosage and administration details:

Radiotherapy of 45-52 Gy will be applied 5 times per week, over a minimum period of 5 weeks. Capecitabine at a dose of 825 mg/m², twice daily or equivalent dose of 5-FU will be given orally, starting at the first day of radiotherapy and given 5 to 7 days per week during the time of radiotherapy.

Arm title	Chemoradiotherapy
Arm description: Radiotherapy of 45-52 Gy will be applied 5 times per week, over a minimum period of 5 weeks. Capecitabine at a dose of 825 mg/m ² , twice daily or equivalent dose of 5-FU will be given orally, starting at the first day of radiotherapy and given 5 to 7 days per week during the time of radiotherapy.	
Arm type	Active comparator
Investigational medicinal product name	Chemoradiotherapy (Radiotherapy+Captecitabine or - Fluorouracil)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radiopharmaceutical precursor, solution
Routes of administration	Not mentioned

Dosage and administration details:

Radiotherapy of 45-52 Gy will be applied 5 times per week, over a minimum period of 5 weeks. Capecitabine at a dose of 825 mg/m², twice daily or equivalent dose of 5-FU will be given orally, starting at the first day of radiotherapy and given 5 to 7 days per week during the time of radiotherapy.

Number of subjects in period 1^[1]	Chemoradiotherapy +Tecemotide (L-BLP25)+CPA	Chemoradiotherapy +Tecemotide (L-BLP25)	Chemoradiotherapy
Started	39	41	42
Completed	39	41	42

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The baseline characteristics are reported for safety analysis set which included all the subjects who received at least one dose of study drug.

Baseline characteristics

Reporting groups

Reporting group title	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA
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Reporting group description:

Single dose of cyclophosphamide 300 milligram per square meter [mg/m^2] to a maximum of 600 milligram [mg] was administered intravenously, 3 days prior to the start of vaccination, followed by weekly subcutaneous vaccinations with tecemotide (L-BLP25) (actual delivered dose was 806 microgram [mcg]) administered concomitantly with chemotherapy for 8 weeks, followed by a 9th subcutaneous vaccination 7 to 11 days prior to surgery.

Reporting group title	Chemoradiotherapy+Tecemotide (L-BLP25)
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Reporting group description:

Weekly subcutaneous vaccinations with tecemotide (L-BLP25) (actual delivered dose was 806 mcg) administered concomitantly with chemotherapy for 8 weeks, followed by a 9th subcutaneous vaccination 7 to 11 days prior to surgery.

Reporting group title	Chemoradiotherapy
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Reporting group description:

Radiotherapy of 45-52 Gy will be applied 5 times per week, over a minimum period of 5 weeks. Capecitabine at a dose of $825 \text{ mg}/\text{m}^2$, twice daily or equivalent dose of 5-FU will be given orally, starting at the first day of radiotherapy and given 5 to 7 days per week during the time of radiotherapy.

Reporting group values	Chemoradiotherapy +Tecemotide (L-BLP25)+CPA	Chemoradiotherapy +Tecemotide (L-BLP25)	Chemoradiotherapy
Number of subjects	39	41	42
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	61.6	62.2	60.3
standard deviation	± 10.74	± 10.12	± 8.77
Gender categorical			
Units: Subjects			
Female	9	14	10
Male	30	27	32

Reporting group values	Total		
Number of subjects	122		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	-		
standard deviation			
Gender categorical			
Units: Subjects			
Female	33		
Male	89		

End points

End points reporting groups

Reporting group title	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA
Reporting group description:	
Single dose of cyclophosphamide 300 milligram per square meter [mg/m^2] to a maximum of 600 milligram [mg] was administered intravenously, 3 days prior to the start of vaccination, followed by weekly subcutaneous vaccinations with tecemotide (L-BLP25) (actual delivered dose was 806 microgram [mcg]) administered concomitantly with chemotherapy for 8 weeks, followed by a 9th subcutaneous vaccination 7 to 11 days prior to surgery.	
Reporting group title	Chemoradiotherapy+Tecemotide (L-BLP25)
Reporting group description:	
Weekly subcutaneous vaccinations with tecemotide (L-BLP25) (actual delivered dose was 806 mcg) administered concomitantly with chemotherapy for 8 weeks, followed by a 9th subcutaneous vaccination 7 to 11 days prior to surgery.	
Reporting group title	Chemoradiotherapy
Reporting group description:	
Radiotherapy of 45-52 Gy will be applied 5 times per week, over a minimum period of 5 weeks. Capecitabine at a dose of $825 \text{ mg}/\text{m}^2$, twice daily or equivalent dose of 5-FU will be given orally, starting at the first day of radiotherapy and given 5 to 7 days per week during the time of radiotherapy.	

Primary: Change from baseline in tumor immune response evaluated by immunohistochemical (IHC) analysis of tumor infiltrating lymphocytes (TILs) at week 14 (post-surgery)

End point title	Change from baseline in tumor immune response evaluated by immunohistochemical (IHC) analysis of tumor infiltrating lymphocytes (TILs) at week 14 (post-surgery)
End point description:	
Tumor biopsy samples were collected prior to baseline and after the surgery. The TILs were evaluated in 3 of the most abundant high-power fields (x40) per sample and the mean value considered (after excluding the lowest and the highest value). The tumor immune response was calculated as number of TILs divided by 100 tumor cells. This endpoint was assessed in immunomonitoring analysis set which included all subjects for whom at least the baseline ELISpot blood and tumor sample, tumor sample at surgery and pre-surgery ELISpot blood drawing were available and whose tumor biopsy at baseline was MUC1-positive. Within the data table, n=number of subjects analyzed for each category.	
End point type	Primary
End point timeframe:	
Baseline and Week 14 (post-surgery)	

End point values	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA	Chemoradiotherapy+Tecemotide (L-BLP25)	Chemoradiotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	33	30	
Units: per 100 tumor cells				
arithmetic mean (standard deviation)				
CD8+ (n=23, 27, 26)	0.609 (\pm 5.4241)	0.543 (\pm 4.5009)	1.538 (\pm 3.9509)	
CD8+/GrB+ (n=23, 27, 26)	0.565 (\pm 3.1646)	0.216 (\pm 2.4187)	0.936 (\pm 2.7649)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Category: CD8+ The difference between baseline and surgical tumor samples was analysed and compared across the 3 treatment arms (effect estimate for Arm A vs Arm C) based on an analysis of covariance (ANCOVA) model. Difference from baseline = Surgery value-Baseline value. Adjustment was based on ANCOVA model with treatment arm as factor and baseline value as covariate. No interaction included. Pairwise tests have been performed to compare Arm A with Arm C, Arm B with Arm C, and Arm A with Arm B	
Comparison groups	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA v Chemoradiotherapy
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.794 ^[1]
Method	type III SS F-test
Parameter estimate	Effect estimate
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.65

Notes:

[1] - Arm effect

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Category: CD8+ The difference between baseline and surgical tumor samples was analysed and compared across the 3 treatment arms (effect estimate for Arm B vs Arm C) based on an ANCOVA model. Difference from baseline = Surgery value-Baseline value. Adjustment was based on ANCOVA model with treatment arm as factor and baseline value as covariate. No interaction included. Pairwise tests have been performed to compare Arm A with Arm C, Arm B with Arm C, and Arm A with Arm B.	
Comparison groups	Chemoradiotherapy+Tecemotide (L-BLP25) v Chemoradiotherapy
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.794 ^[2]
Method	type III SS F-test
Parameter estimate	Effect estimate
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	0.43

Notes:

[2] - Arm effect

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Category: CD8+ The difference between baseline and surgical tumor samples was analysed and compared across the 3 treatment arms (effect estimate for Arm A vs Arm B) based on an ANCOVA model. Difference from baseline = Surgery value-Baseline value. Adjustment was based on ANCOVA model with treatment arm as factor and baseline value as covariate. No interaction included. Pairwise tests have been performed to compare Arm A with Arm C, Arm B with Arm C, and Arm A with Arm B.	
Comparison groups	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA v Chemoradiotherapy+Tecemotide (L-BLP25)
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.794 ^[3]
Method	type III SS F-test
Parameter estimate	Effect estimate
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.82

Notes:

[3] - Arm effect

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Category: CD8+/GrB+ The difference between baseline and surgical tumor samples was analysed and compared across the 3 treatment arms (effect estimate for Arm A vs Arm C) based on an ANCOVA model. Difference from baseline = Surgery value-Baseline value. Adjustment was based on ANCOVA model with treatment arm as factor and baseline value as covariate. No interaction included. Pairwise tests have been performed to compare Arm A with Arm C, Arm B with Arm C, and Arm A with Arm B.	
Comparison groups	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA v Chemoradiotherapy
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.654 ^[4]
Method	type III SS F-test
Parameter estimate	Effect estimate
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	0.57

Notes:

[4] - Arm effect

Statistical analysis title	Statistical Analysis 5
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Statistical analysis description:

Category: CD8+/GrB+ The difference between baseline and surgical tumor samples was analysed and compared across the 3 treatment arms (effect estimate for Arm B vs Arm C) based on an ANCOVA model. Difference from baseline = Surgery value-Baseline value. Adjustment was based on ANCOVA model with treatment arm as factor and baseline value as covariate. No interaction included. Pairwise tests have been performed to compare Arm A with Arm C, Arm B with Arm C, and Arm A with Arm B.

Comparison groups	Chemoradiotherapy+Tecemotide (L-BLP25) v Chemoradiotherapy
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.654 ^[5]
Method	type III SS F-test
Parameter estimate	Effect estimate
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	0.31

Notes:

[5] - Arm effect

Statistical analysis title	Statistical Analysis 6
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Statistical analysis description:

Category: CD8+/GrB+ The difference between baseline and surgical tumor samples was analysed and compared across the 3 treatment arms (effect estimate for Arm A vs Arm B) based on an ANCOVA model. Difference from baseline = Surgery value-Baseline value. Adjustment was based on ANCOVA model with treatment arm as factor and baseline value as covariate. No interaction included. Pairwise tests have been performed to compare Arm A with Arm C, Arm B with Arm C, and Arm A with Arm B.

Comparison groups	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA v Chemoradiotherapy+Tecemotide (L-BLP25)
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.654 ^[6]
Method	type III SS F-test
Parameter estimate	Effect estimate
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.74

Notes:

[6] - Arm effect

Primary: Immunological response to treatment in relation to microsatellite instability (MSI) status: number of subjects per MSI category

End point title	Immunological response to treatment in relation to microsatellite instability (MSI) status: number of subjects per MSI category
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End point description:

A potential association between MSI status (present or absent) and the primary endpoints (difference

from baseline to surgery in CD8+ and CD8+/GrB+ T cell infiltration) was evaluated. This endpoint was assessed in immunomonitoring analysis set which included all subjects for whom at least the baseline ELISpot blood and tumor sample, tumor sample at surgery and pre-surgery ELISpot blood drawing were available and whose tumor biopsy at baseline was MUC1-positive.

End point type	Primary
End point timeframe:	
18 weeks	

End point values	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA	Chemoradiotherapy+Tecemotide (L-BLP25)	Chemoradiotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	33	30	
Units: Subjects				
No	25	32	30	
Yes	2	1	0	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Category: CD8+ The difference in T cell infiltration from baseline to surgery was analysed and compared across the 3 treatment arms (effect estimate for Arm A vs Arm C) based on an ANCOVA model. Difference from baseline = Surgery value-Baseline value. Adjustment was based on ANCOVA model with treatment arm as factor and baseline value and MSI category as covariates. No interaction included. Pairwise tests have been performed to compare Arm A with Arm C, Arm B with Arm C, and Arm A with Arm B.

Comparison groups	Chemoradiotherapy v Chemoradiotherapy+Tecemotide (L-BLP25)+CPA
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.921
Method	type III SS F-test
Parameter estimate	Estimate
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	0.67

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Category: CD8+ The difference in T cell infiltration from baseline to surgery was analysed and compared across the 3 treatment arms (effect estimate for Arm B vs Arm C) based on an ANCOVA model. Difference from baseline = Surgery value-Baseline value. Adjustment was based on ANCOVA model with

treatment arm as factor and baseline value and MSI category as covariates. No interaction included. Pairwise tests have been performed to compare Arm A with Arm C, Arm B with Arm C, and Arm A with Arm B.

Comparison groups	Chemoradiotherapy+Tecemotide (L-BLP25) v Chemoradiotherapy
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.921
Method	type III SS F-test
Parameter estimate	Estimate
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	0.44

Statistical analysis title	Statistical Analysis 3
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Statistical analysis description:

Category: CD8+ The difference in T cell infiltration from baseline to surgery was analysed and compared across the 3 treatment arms (effect estimate for Arm A vs Arm B) based on an ANCOVA model. Difference from baseline = Surgery value-Baseline value. Adjustment was based on ANCOVA model with treatment arm as factor and baseline value and MSI category as covariates. No interaction included. Pairwise tests have been performed to compare Arm A with Arm C, Arm B with Arm C, and Arm A with Arm B.

Comparison groups	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA v Chemoradiotherapy+Tecemotide (L-BLP25)
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.921
Method	type III SS F-test
Parameter estimate	Estimate
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.83

Statistical analysis title	Statistical Analysis 4
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Statistical analysis description:

Category:CD8+/GrB+ The difference in T cell infiltration from baseline to surgery was analysed and compared across the 3 treatment arms (effect estimate for Arm A vs Arm C) based on an ANCOVA model. Difference from baseline=Surgery value-Baseline value. Adjustment was based on ANCOVA model with treatment arm as factor and baseline value and MSI category as covariates. No interaction included. Pairwise tests have been performed to compare Arm A with Arm C, Arm B with Arm C, and Arm A with Arm B.

Comparison groups	Chemoradiotherapy v Chemoradiotherapy+Tecemotide (L-BLP25)+CPA
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Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.89
Method	type III SS F-test
Parameter estimate	Estimate
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.58

Statistical analysis title	Statistical Analysis 5
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Statistical analysis description:

Category: CD8+/GrB+ The difference in T cell infiltration from baseline to surgery was analysed and compared across the 3 treatment arms (effect estimate for Arm B vs Arm C) based on an ANCOVA model. Difference from baseline=Surgery value-Baseline value. Adjustment was based on ANCOVA model with treatment arm as factor and baseline value and MSI category as covariates. No interaction included. Pairwise tests have been performed to compare Arm A with Arm C, Arm B with Arm C, and Arm A with Arm B.

Comparison groups	Chemoradiotherapy+Tecemotide (L-BLP25) v Chemoradiotherapy
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.89
Method	type III SS F-test
Parameter estimate	Estimate
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.31

Statistical analysis title	Statistical Analysis 6
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Statistical analysis description:

Category: CD8+/GrB+ The difference in T cell infiltration from baseline to surgery was analysed and compared across the 3 treatment arms (effect estimate for Arm A vs Arm B) based on an ANCOVA model. Difference from baseline=Surgery value-Baseline value. Adjustment was based on ANCOVA model with treatment arm as factor and baseline value and MSI category as covariates. No interaction included. Pairwise tests have been performed to compare Arm A with Arm C, Arm B with Arm C, and Arm A with Arm B.

Comparison groups	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA v Chemoradiotherapy+Tecemotide (L-BLP25)
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Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.89
Method	type III SS F-test
Parameter estimate	Estimate
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.74

Primary: Change from baseline in interferon (IFN)-gamma secretion of mononuclear cells in response to MUC-1 by enzyme-linked immunosorbent spot (ELISpot) at post-baseline

End point title	Change from baseline in interferon (IFN)-gamma secretion of mononuclear cells in response to MUC-1 by enzyme-linked immunosorbent spot (ELISpot) at post-baseline ^[7]
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End point description:

IFN-gamma secretion of mononuclear cells in response to MUC1 was to be measured by ELISpot. The maximal post-baseline value out of Week 5, Week 11-13 (pre-surgery), and Week 16-18 (follow-up / end-of trial) was evaluated in comparison to Baseline.

End point type	Primary
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End point timeframe:

Baseline, Week 5, Week 13 (pre-surgery), and Week 18 (end-of trial)

Notes:

[7] - 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: Data was not analyzed as no acceptable ELISpot assay was available.

End point values	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA	Chemoradiotherapy+Tecemotide (L-BLP25)	Chemoradiotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[8]	0 ^[9]	0 ^[10]	
Units: Subjects				

Notes:

[8] - Data were not analyzed as no acceptable ELISpot assay was available.

[9] - Data were not analyzed as no acceptable ELISpot assay was available.

[10] - Data were not analyzed as no acceptable ELISpot assay was available.

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in IFN-gamma secretion of mononuclear cells in response to carcinoembryonic antigen (CEA) by ELISpot at post-baseline

End point title	Change from baseline in IFN-gamma secretion of mononuclear cells in response to carcinoembryonic antigen (CEA) by ELISpot at post-baseline ^[11]
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End point description:

IFN-gamma secretion of mononuclear cells in response to CEA was to be measured by ELISpot. The maximal post-baseline value out of Week 5, Week 11-13 (pre-surgery), and Week 16-18 (follow-up / end-of trial) was evaluated in comparison to Baseline.

End point type Primary

End point timeframe:

Baseline, Week 5, Week 13 (pre-surgery), and Week 18 (end-of trial)

Notes:

[11] - 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: Data was not analyzed as no acceptable ELISpot assay was available.

End point values	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA	Chemoradiotherapy+Tecemotide (L-BLP25)	Chemoradiotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[12]	0 ^[13]	0 ^[14]	
Units: Subjects				

Notes:

[12] - Data were not analyzed as no acceptable ELISpot assay was available.

[13] - Data were not analyzed as no acceptable ELISpot assay was available.

[14] - Data were not analyzed as no acceptable ELISpot assay was available.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in peritumoral immune response at week 14 (post-surgery)

End point title Change from baseline in peritumoral immune response at week 14 (post-surgery)

End point description:

Ki67+CD3+ T cells; regulatory T cells (FOXP3+) and myeloid-derived suppressor cells (CD33+CD14-); other immune cells such as NK cells (CD3-CD57+), B cells (CD20+), macrophages (CD68+), and dendritic cells (S100+). Peritumoral immune response was calculated as number of lymphoid cells at the margin of the tumor or in the tumor bed (if there is complete pathological response). The number "99999" in the arithmetic mean and standard deviation indicate that no parameters were identified with a p-value less than (<) 0.05 for either arm or interaction effect. Thus, no summary statistics are provided for the difference from baseline in IHC parameters for the immunomonitoring analysis set.

End point type Secondary

End point timeframe:

Baseline and Week 14 (post-surgery)

End point values	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA	Chemoradiotherapy+Tecemotide (L-BLP25)	Chemoradiotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	33	30	
Units: mg/mL				
arithmetic mean (standard deviation)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in immunological response in peripheral blood at week 18 (follow-up / end-of trial)

End point title	Change from baseline in immunological response in peripheral blood at week 18 (follow-up / end-of trial)
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End point description:

Immunological changes in peripheral blood were evaluated based on fluorescence analysis cell sorter phenotypic characterization of T cells (CD3+CD4+ and CD3+CD8+) and of markers of activation and proliferation (CD27, BTLA); and regulatory cells such as CD3+CD4+ (or CD8+) CD45RA+CD25+FoxP3+CD127 T cells. Immunological Response in peripheral blood was measured on a continuous scale. This endpoint was assessed in immunomonitoring analysis set which included all subjects for whom at least the baseline ELISpot blood and tumor sample, tumor sample at surgery and pre-surgery ELISpot blood drawing were available and whose tumor biopsy at baseline was MUC1-positive. Within the data table, n=number of subjects analysed for each category.

End point type	Secondary
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End point timeframe:

Baseline and Week 18 (follow-up / end-of trial)

End point values	Chemoradiotherapy+Tecemotide (L-BLP25)+CPA	Chemoradiotherapy+Tecemotide (L-BLP25)	Chemoradiotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	33	30	
Units: Log2 (%)				
arithmetic mean (standard deviation)				
CD3-CD56+CD16+GranzymeB+ (n=26,30,24)	-0.013 (± 0.1051)	-0.046 (± 0.1259)	-0.081 (± 0.2238)	
CD3-CD56+CD16+Perforin+ (n=26,30,24)	-0.05 (± 0.0769)	-0.033 (± 0.1868)	-0.088 (± 0.2282)	
CD3+CD4+CD27+ (n=26,30,24)	-0.181 (± 0.1848)	-0.135 (± 0.1521)	-0.099 (± 0.1913)	
CD3-CD56+CD16+Granzyme B+/LY (n=26,30,24)	0.264 (± 0.5885)	0.047 (± 1.2787)	0.415 (± 0.604)	
CD3-CD56+CD16+Perforin+/LY (n=26,30,24)	0.226 (± 0.5669)	0.058 (± 1.2902)	0.411 (± 0.6019)	
CD3-CD56+CD16-CD107a+ (n=26,30,24)	0.216 (± 1.201)	-0.318 (± 1.5863)	0.037 (± 1.0191)	
CD3+CD8+CD127-FoxP3-CD45RA-CD25+CTLA4+ (n=27,29,24)	0.05 (± 0.3933)	0.152 (± 0.5386)	-0.012 (± 0.5202)	
CD3+CD56+CD16-Granzyme B+ (n=26,30,24)	0.479 (± 1.6943)	-0.241 (± 0.9628)	-0.024 (± 0.6623)	
CD3-CD56+CD16+/LY (n=26,30,24)	0.277 (± 0.5448)	0.09 (± 1.2968)	0.497 (± 0.6119)	
CD3-CD19+BTLA4+ (n=27,29,23)	-0.03 (± 0.0489)	-0.028 (± 0.055)	-0.017 (± 0.0352)	

Lymphs Tube 2 (n=27,30,25)	-1.024 (± 0.4392)	-0.941 (± 0.608)	-0.952 (± 0.4761)	
CD3+CD56+CD16+CD107a+ (n=26,30,24)	-1.216 (± 4.5484)	1.966 (± 6.6322)	-2.752 (± 6.479)	
CD3+CD4+BTLA4+ (n=26,30,24)	0.063 (± 1.4413)	0.122 (± 0.4833)	-0.035 (± 0.4117)	
Lymphs Tube 3 (n=27,30,25)	-0.994 (± 0.4545)	-0.92 (± 0.5923)	-0.936 (± 0.4746)	
CD3+CD56+CD16+CCR7+ (n=26,30,24)	-1.341 (± 4.1442)	0.541 (± 6.3502)	-3.39 (± 5.1877)	
CD3+CD8+CD127+FoxP3-CD25- CD45RA+CTLA4- (n=27,29,24)	-0.604 (± 0.8102)	-1.062 (± 1.1436)	-0.94 (± 1.2678)	
Background corrected CD3+CD4+IFNg+ (n=21,27,21)	0.058 (± 0.9767)	0.544 (± 0.9521)	0.359 (± 1.3187)	
CD3+CD56+CD16+Granzyme B+/LY (n=26,30,24)	0.243 (± 0.6969)	-0.201 (± 1.0731)	0.131 (± 0.7652)	
CD3+CD56+CD16+Perforin+/LY (n=26,30,24)	0.24 (± 0.6997)	-0.177 (± 0.992)	0.101 (± 0.7617)	
CD3+CD4+CD127+FoxP3-CD45RA- CD25+CTLA4+ (n=27,29,24)	0.711 (± 1.3825)	0.674 (± 1.2689)	1.035 (± 1.4996)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Date of first signature of informed consent until the End of Trial visit.

Adverse event reporting additional description:

Treatment emergent AEs were defined as those that emerged during treatment, having been absent pretreatment, or worsened relative to the pretreatment state, and with onset dates occurring from the first trial treatment until the End of Trial visit.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	Chemoradiotherapy+Tecemotide (LBLP25)+ CPA
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Reporting group description:

Single dose of cyclophosphamide (300 mg/m² to a maximum of 600 mg) was administered intravenously, 3 days prior to the start of vaccination, followed by weekly subcutaneous vaccinations with tecemotide (LBLP25) (actual delivered dose was 806 mcg) administered concomitantly with chemotherapy for 8 weeks, followed by a 9th subcutaneous vaccination 7 to 11 days prior to surgery.

Reporting group title	Chemoradiotherapy
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Reporting group description:

Radiotherapy of 45-52 Gy will be applied 5 times per week, over a minimum period of 5 weeks. Capecitabine at a dose of 825 mg/m², twice daily or equivalent dose of 5FU was given orally, starting at the first day of radiotherapy and given 5 to 7 days per week during the time of radiotherapy.

Reporting group title	Chemoradiotherapy+Tecemotide (LBLP25)
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Reporting group description:

Weekly subcutaneous vaccinations with tecemotide (LBLP25) (actual delivered dose was 806 mcg) administered concomitantly with chemotherapy for 8 weeks, followed by a 9th subcutaneous vaccination 7 to 11 days prior to surgery.

Serious adverse events	Chemoradiotherapy + Tecemotide (LBLP25)+ CPA	Chemoradiotherapy	Chemoradiotherapy + Tecemotide (LBLP25)
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 39 (25.64%)	12 / 42 (28.57%)	10 / 41 (24.39%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Peritumoural oedema			
subjects affected / exposed	0 / 39 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic thrombosis			

subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site reaction			
subjects affected / exposed	1 / 39 (2.56%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	1 / 39 (2.56%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 39 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 39 (2.56%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic leak			
subjects affected / exposed	0 / 39 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal anastomotic leak			
subjects affected / exposed	1 / 39 (2.56%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stoma complication			
subjects affected / exposed	2 / 39 (5.13%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural intestinal perforation			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Radiation skin injury			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Central nervous system lesion			
subjects affected / exposed	0 / 39 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiplegia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulopathy			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Gastrointestinal necrosis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 39 (2.56%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 39 (2.56%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal haemorrhage			
subjects affected / exposed	1 / 39 (2.56%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 39 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Coccydynia			

subjects affected / exposed	0 / 39 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 39 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 39 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection bacterial			
subjects affected / exposed	0 / 39 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 39 (0.00%)	1 / 42 (2.38%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Chemoradiotherapy +Tecemotide (LBLP25)+ CPA	Chemoradiotherapy	Chemoradiotherapy +Tecemotide (LBLP25)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 39 (97.44%)	41 / 42 (97.62%)	41 / 41 (100.00%)
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 39 (2.56%)	3 / 42 (7.14%)	1 / 41 (2.44%)
occurrences (all)	1	3	1
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	9 / 39 (23.08%)	6 / 42 (14.29%)	7 / 41 (17.07%)
occurrences (all)	9	6	7
Chills			
subjects affected / exposed	4 / 39 (10.26%)	1 / 42 (2.38%)	2 / 41 (4.88%)
occurrences (all)	4	1	2
Fatigue			
subjects affected / exposed	12 / 39 (30.77%)	12 / 42 (28.57%)	9 / 41 (21.95%)
occurrences (all)	12	12	9
Influenza like illness			
subjects affected / exposed	4 / 39 (10.26%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	4	0	0
Injection site erythema			
subjects affected / exposed	3 / 39 (7.69%)	0 / 42 (0.00%)	11 / 41 (26.83%)
occurrences (all)	3	0	11
Injection site haematoma			
subjects affected / exposed	2 / 39 (5.13%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences (all)	2	0	1
Injection site induration			
subjects affected / exposed	4 / 39 (10.26%)	0 / 42 (0.00%)	2 / 41 (4.88%)
occurrences (all)	4	0	2
Injection site nodule			
subjects affected / exposed	5 / 39 (12.82%)	0 / 42 (0.00%)	11 / 41 (26.83%)
occurrences (all)	5	0	11
Injection site pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 42 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	3
Injection site reaction			
subjects affected / exposed	7 / 39 (17.95%)	3 / 42 (7.14%)	7 / 41 (17.07%)
occurrences (all)	7	3	7
Pyrexia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences (all)	2	1	1
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	2 / 42 (4.76%) 2	2 / 41 (4.88%) 2
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	4 / 42 (9.52%) 4	1 / 41 (2.44%) 1
Insomnia subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	2 / 42 (4.76%) 2	4 / 41 (9.76%) 4
Investigations			
Weight decreased subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3	5 / 42 (11.90%) 5	2 / 41 (4.88%) 2
Antinuclear antibody increased subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 4	0 / 42 (0.00%) 0	3 / 41 (7.32%) 3
Injury, poisoning and procedural complications			
Procedural nausea subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	3 / 42 (7.14%) 3	2 / 41 (4.88%) 2
Procedural pain subjects affected / exposed occurrences (all)	8 / 39 (20.51%) 8	7 / 42 (16.67%) 7	3 / 41 (7.32%) 3
Radiation skin injury subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	2 / 42 (4.76%) 2	9 / 41 (21.95%) 9
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	0 / 42 (0.00%) 0	3 / 41 (7.32%) 3
Dysgeusia subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3	1 / 42 (2.38%) 1	2 / 41 (4.88%) 2
Headache			

subjects affected / exposed occurrences (all)	6 / 39 (15.38%) 6	4 / 42 (9.52%) 4	1 / 41 (2.44%) 1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 39 (12.82%)	6 / 42 (14.29%)	4 / 41 (9.76%)
occurrences (all)	5	6	4
Leukopenia			
subjects affected / exposed	4 / 39 (10.26%)	5 / 42 (11.90%)	5 / 41 (12.20%)
occurrences (all)	4	5	5
Neutropenia			
subjects affected / exposed	2 / 39 (5.13%)	2 / 42 (4.76%)	1 / 41 (2.44%)
occurrences (all)	2	2	1
Thrombocytopenia			
subjects affected / exposed	1 / 39 (2.56%)	4 / 42 (9.52%)	0 / 41 (0.00%)
occurrences (all)	1	4	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 39 (2.56%)	3 / 42 (7.14%)	3 / 41 (7.32%)
occurrences (all)	1	3	3
Abdominal pain			
subjects affected / exposed	5 / 39 (12.82%)	8 / 42 (19.05%)	8 / 41 (19.51%)
occurrences (all)	5	8	8
Abdominal pain upper			
subjects affected / exposed	2 / 39 (5.13%)	0 / 42 (0.00%)	5 / 41 (12.20%)
occurrences (all)	2	0	5
Anorectal discomfort			
subjects affected / exposed	5 / 39 (12.82%)	7 / 42 (16.67%)	3 / 41 (7.32%)
occurrences (all)	5	7	3
Constipation			
subjects affected / exposed	6 / 39 (15.38%)	7 / 42 (16.67%)	4 / 41 (9.76%)
occurrences (all)	6	7	4
Defaecation urgency			
subjects affected / exposed	2 / 39 (5.13%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences (all)	2	1	1
Diarrhoea			

subjects affected / exposed	15 / 39 (38.46%)	21 / 42 (50.00%)	18 / 41 (43.90%)
occurrences (all)	15	21	18
Dyspepsia			
subjects affected / exposed	2 / 39 (5.13%)	3 / 42 (7.14%)	1 / 41 (2.44%)
occurrences (all)	2	3	1
Flatulence			
subjects affected / exposed	2 / 39 (5.13%)	3 / 42 (7.14%)	3 / 41 (7.32%)
occurrences (all)	2	3	3
Faecal incontinence			
subjects affected / exposed	2 / 39 (5.13%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences (all)	2	0	1
Gastrointestinal pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	8 / 39 (20.51%)	13 / 42 (30.95%)	12 / 41 (29.27%)
occurrences (all)	8	13	12
Painful defaecation			
subjects affected / exposed	3 / 39 (7.69%)	4 / 42 (9.52%)	1 / 41 (2.44%)
occurrences (all)	3	4	1
Proctalgia			
subjects affected / exposed	10 / 39 (25.64%)	12 / 42 (28.57%)	14 / 41 (34.15%)
occurrences (all)	10	12	14
Rectal haemorrhage			
subjects affected / exposed	5 / 39 (12.82%)	4 / 42 (9.52%)	2 / 41 (4.88%)
occurrences (all)	5	4	2
Rectal tenesmus			
subjects affected / exposed	2 / 39 (5.13%)	0 / 42 (0.00%)	2 / 41 (4.88%)
occurrences (all)	2	0	2
Toothache			
subjects affected / exposed	1 / 39 (2.56%)	0 / 42 (0.00%)	3 / 41 (7.32%)
occurrences (all)	1	0	3
Vomiting			
subjects affected / exposed	6 / 39 (15.38%)	2 / 42 (4.76%)	4 / 41 (9.76%)
occurrences (all)	6	2	4
Skin and subcutaneous tissue disorders			

Dermatitis			
subjects affected / exposed	2 / 39 (5.13%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences (all)	2	0	1
Dry skin			
subjects affected / exposed	2 / 39 (5.13%)	1 / 42 (2.38%)	2 / 41 (4.88%)
occurrences (all)	2	1	2
Erythema			
subjects affected / exposed	5 / 39 (12.82%)	1 / 42 (2.38%)	5 / 41 (12.20%)
occurrences (all)	5	1	5
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 39 (7.69%)	3 / 42 (7.14%)	4 / 41 (9.76%)
occurrences (all)	3	3	4
Pruritus			
subjects affected / exposed	2 / 39 (5.13%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences (all)	2	0	1
Rash			
subjects affected / exposed	5 / 39 (12.82%)	0 / 42 (0.00%)	4 / 41 (9.76%)
occurrences (all)	5	0	4
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	10 / 39 (25.64%)	5 / 42 (11.90%)	8 / 41 (19.51%)
occurrences (all)	10	5	8
Haematuria			
subjects affected / exposed	2 / 39 (5.13%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences (all)	2	1	1
Pollakiuria			
subjects affected / exposed	3 / 39 (7.69%)	1 / 42 (2.38%)	5 / 41 (12.20%)
occurrences (all)	3	1	5
Urinary tract pain			
subjects affected / exposed	2 / 39 (5.13%)	1 / 42 (2.38%)	2 / 41 (4.88%)
occurrences (all)	2	1	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 39 (0.00%)	4 / 42 (9.52%)	0 / 41 (0.00%)
occurrences (all)	0	4	0
Infections and infestations			

Cystitis			
subjects affected / exposed	3 / 39 (7.69%)	2 / 42 (4.76%)	2 / 41 (4.88%)
occurrences (all)	3	2	2
Nasopharyngitis			
subjects affected / exposed	0 / 39 (0.00%)	3 / 42 (7.14%)	2 / 41 (4.88%)
occurrences (all)	0	3	2
Urinary tract infection			
subjects affected / exposed	2 / 39 (5.13%)	3 / 42 (7.14%)	4 / 41 (9.76%)
occurrences (all)	2	3	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 39 (17.95%)	13 / 42 (30.95%)	6 / 41 (14.63%)
occurrences (all)	7	13	6
Hypokalaemia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences (all)	2	1	1
Hyponatraemia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences (all)	2	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 November 2011	In this amendment, the description of the dose of tecemotide administered under protocol EMR 63325-013 (SPRINT) was corrected from 930 mcg to 806 mcg to more accurately reflect the actual quantity of drug administered to subjects.
02 November 2012	In this amendment, the definitions of AEs/SAEs associated with disease progression and SAEs related to trial treatment were updated; the acceptable time frames for imaging and tecemotide administration were modified; total blood volume collected for biochemistry and overall was adjusted; list of markers for the biomarker assessments was clarified.

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.

Not all efficacy data were analyzed as no acceptable ELISpot assay is available. The Sponsor decided to discontinue the development of tecemotide (L-BLP25) in September 2014.

Notes: