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

CLINICAL STUDY REPORT

Document status	FINAL Version 3.0
Sponsor's protocol code	LICC01
EudraCT registration number	2011-000218-20
Sponsor	[redacted] Mainz University Medical Center, Germany
Coordinating Investigator	[redacted]
Medical Director at iOMEDICO	[redacted]
Team Leader at iOMEDICO	[redacted]
Project Leader at iOMEDICO	[redacted]
Date of final study report	29-NOV-2018

This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

1. Title Page

Study Title	**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**
Study Title German	LICC: L-BLP25 bei Patienten mit kolorektalem Karzinom nach kurativer Lebermetastasenresektion – eine randomisierte, plazebokontrollierte, multizentrische, multinationale, doppelblinde Phase II Studie
Short Title	L-BLP25 In Colorectal Cancer (LICC)
Protocol No.	LICC01
EudraCT No.	2011-000218-20
Name of Test Drug/Product	L-BLP25 (Tecemotide)
Comparator	Placebo
Dosage (Strength)	L-BLP25 930 µg in 4 vials per treatment (4 x 0.5 mL) 300 mg/m² (to a maximum of 600 mg) cyclophosphamide once 3 days before the first L-BLP25 administration
Indication	Metastatic colorectal cancer (CRC) after curative-intent resection of hepatic metastases
Design	Randomized (2:1), placebo-controlled, multicenter, multinational, double-blinded
Development Phase	Phase II
Sponsor	[redacted] Mainz University Medical Center, Germany
Coordinating Investigator	[redacted]
Author of Report	[redacted]
Manufacturer of Investigational Product	Merck KGaA, Darmstadt, Germany
First Patient In	21-OCT-2011
Study Completion Date	24-JAN-2018
Version and Date of Report	FINAL Version 3.0 dated 29-NOV-2018

2. Synopsis

Name of Sponsor/Company: [redacted] Mainz University Medical Center, Germany	Volume: Page:	(For National Authority Use Only)
Name of Finished Product: L-BLP25 (Tecemotide)		
Name of Active Ingredient: L-BLP25		

Title of study:
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

Coordinating investigator:
[redacted]

Study center(s):
Twenty-five centers in Europe were initiated, 22 centers recruited patients (21 in Germany, 1 in Austria).

Publications (reference):
Full publication:
Schimanski CC, Möhler M, Schön M, van Cutsem E, Greil R, Bechstein WO, et al. 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. BMC Cancer. 2012 Apr 11;12:144.
Presentation at ASCO congresses:
Schimanski CC, Galle PR, Lang H, Schoen M, Moehler MH. LICC: L-BLP25 in patients with colorectal carcinoma after curative resection of hepatic metastases—A randomized, double-blind, placebo-controlled, multicenter, multinational, phase II trial. J Clin Oncol. 2011 May 20;29(15_suppl):TPS166-TPS166.
Schimanski CC, Moehler MH, Lang H, Schoen M, Smith-Machnow V, Kanzler S, et al. A randomized, double-blind, placebo-controlled, multicenter, multinational, phase II trial of L-BLP25 in patients with colorectal carcinoma following R0/R1 hepatic metastasectomy. J Clin Oncol. 2012 May 20;30(15_suppl):TPS3641-TPS3641.
Kasper S, Overkamp F, Moehler MH, Kullmann F, Lang H, Schoen M, et al. A randomized, double-blind, placebo-controlled, multicenter, multinational, phase II trial immunotherapy with L-BLP25 (tecemotide) in patients with colorectal carcinoma following R0/R1 hepatic metastasectomy. J Clin Oncol. 2013 May 20;31(15_suppl):TPS3124-TPS3124.
Kasper S, Moehler M, Hegewisch-Becker S, Overkamp F, Bechstein WO, Kullmann F, et al. A randomized, double-blind, placebo-controlled, multicenter, binational, phase II trial of immunotherapy with L-BLP25 (tecemotide) in patients with colorectal carcinoma following R0/R1 hepatic metastasectomy. J Clin Oncol. 2014 May 20;32(15_suppl):TPS3658-TPS3658.
abstract submitted for presentation at ASCO GI 2019: Schimanski C, Kasper S, Hegewisch-Becker S, Schröder J, Overkamp F, Kullmann F, et al. A randomized, double-blinded, placebo-controlled multicenter phase II trial of adjuvant immunotherapy with tecemotide (L-BLP25) after R0/R1 hepatic colorectal cancer metastasectomy (LICC): Final results.
Moehler M, Folprecht G, Heinemann V, Holch J, Maderer A, Kasper S, et al. Survival after secondary liver resection in metastatic colorectal cancer: A comparative analysis of the LICC trial with historical controls (CELIM, FIRE-3)

Studied period (years): 5 years and 2 months First patient in: 21-OCT-2011 Last patient out: 30-DEC-2016	**Phase of development**: Phase II

Objectives:
Primary objective:
- Comparative evaluation of recurrence-free survival (RFS) time and 3-year overall survival (OS)

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time between the treatment groups (L-BLP25 plus cyclophosphamide versus placebo and saline infusion)

Secondary objectives:

- Safety and tolerability
- RFS in the subgroup of mucin - (MUC1) positive cancers
- OS in a subgroup of MUC1 positive cancers

Exploratory objectives:

- MUC1 expression analysis and immuno-monitoring parameters to be defined in separate translational protocol (not part of this report)

Methodology:

Randomized, placebo-controlled, multicenter, double-blinded, efficacy/safety study of L-BLP25 in patients with fully-resected metastatic colorectal carcinoma (CRC). Eligible patients had their primary tumor resected and had undergone curative-intent resection of liver metastases within the last 8 weeks. Eligible patients were randomized to treatment with L-BLP25 immunotherapy + cyclophosphamide versus placebo + saline (2:1). Treatment was discontinued upon documented relapse or if patients were free of relapse; otherwise, treatment was discontinued 2 years after randomization.

Number of patients	**planned (Amendment III)**: 120 patients (80 in the L-BLP25 arm, 40 in the placebo arm) **screened**: 133 patients	**randomized**: 121 patients (79 to L-BLP25, 42 to placebo) **completed**: 107 patients	**analyzed for efficacy**: 121 patients (79 receiving L-BLP25, 42 receiving placebo) **analyzed for safety**: 121 patients (79 receiving L-BLP25, 42 receiving placebo)

Diagnosis and main criteria for inclusion:

This trial was designed for patients with metastatic CRC, who had undergone a complete resection of their primary tumor and recent resection of their liver metastases (R0 or R1) with curative intent.

Inclusion criteria:

- Signed written informed consent.
- Male or female.
- At least 18 years of age.
- Female patients of child-bearing potential (and if appropriate, male patients with female partners of child-bearing potential) willing to use an adequate method of contraception for 4 weeks prior to, during and 12 weeks after the last dose of trial medication. A negative pregnancy test was required for female patients. Adequate contraception was defined as two barrier methods, or one barrier method with a spermicide or intrauterine device, or use of hormonal female contraceptive. Women of child-bearing potential were defined as: “All female patients after puberty unless they are postmenopausal for at least 2 years, are surgically sterile or are sexually inactive.”
- Histologically confirmed diagnosis of adenocarcinoma of the colon or rectum with complete resection of primary tumor and no evidence of local relapse.
- Metastatic disease of the liver, with recent (< 8 weeks prior to randomization) both primary and secondary resection (R0 or R1) of all liver metastases. Metastectomy could have been either synchronous or metachronous. Neoadjuvant therapy could have been applied prior to metastectomy.
- Patient had a colonoscopy or rectoscopy within the last 3 months prior to initiation of therapy
- Patient had an ECOG performance status of 0 or 1.

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- Patient had adequate hematologic, hepatic, and renal function within 2 weeks prior to initiation of therapy as defined by the following:
  - Absolute neutrophil count > 1,500/mm³ and platelets > 140,000/mm³.
  - Bilirubin < 1.5 x upper limit of normal (ULN).
  - Aspartate transaminase (AST) and alanine transaminase (ALT) < 2.5 x ULN.
  - Creatinine < 1.5 x ULN.
  - International normalized ratio (INR) and partial thromboplastin time (PTT) within normal range and within therapeutic range, respectively, in case of anticoagulation.
- Willingness to comply with study protocol requirements.

Test product, dose and mode of administration, batch number:
L-BLP25 (tecemotide) was supplied as a sterile lyophilized powder to be reconstituted with 0.6 mL 0.9% sodium chloride in a 5 mL glass vial. One treatment consisted of 4 subcutaneous (s.c.) injections (each 0.5 mL). Patient was injected with L-BLP25 2.0 mL in total per treatment (4 x 0.5 mL), provided in 4 vials (0.5 mL per vial). A single intravenous (i.v.) infusion of 300 mg/m² of cyclophosphamide (CP) was given 3 days before first L-BLP25 treatment. The maximum allowable absolute dose of CP was 600 mg. For batch numbers, see Appendix 16.1.6.

Duration of treatment:
- **Primary treatment phase**: Eight consecutive weekly treatments with L-BLP25 2.0 m L s.c. or placebo at weeks 1, 2, 3, 4, 5, 6, 7, and 8.
- **Maintenance treatment phase**: L-BLP25 2 mL s.c. at 6-week intervals during year 1 and 2, commencing 6 weeks after the end of the primary treatment phase until documentation of recurrence or for a maximum of 2 years after randomization.

Reference therapy, dose and mode of administration, batch number:
The placebo was a sterile lyophilized preparation to be reconstituted with 0.6 mL 0.9% sodium chloride in a 5 mL glass vial and was formulated to provide the same carrier lipid matrix as the immunotherapy but without the monophosphoryl lipid A (MPL) and the MUC1 lipopeptide BLP25. The vial contained 13.63 mg of 3 lipids: cholesterol, dimyristoyl phosphatidylglycerol (DMPG) and dipalmitoyl phosphatidylcholine (DPPC) in a 5 mL glass vial.

Patients in the placebo arm received a single i.v. infusion of saline 3 days before the first placebo injection. Patient was injected with placebo 2.0 mL in total per treatment (4 x 0.5 mL) provided in 4 vials (0.5 mL per vial). For batch numbers, see Appendix 16.1.6.

Criteria for evaluation:

Efficacy:

Primary endpoint
- RFS based on standard imaging and OS

Secondary endpoints:
- RFS of patients with MUC1 positive cancers
- OS of patients with MUC1 positive cancers

Safety:
- Incidence and type of adverse events (AEs)
- Vital signs and clinical laboratory assessments
- Injection site reactions (ISRs)

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Statistical methods:

The main objective of the trial was to examine RFS and 3-year OS. Any statistical analysis is regarded as fully exploratory but appropriate to show a trend towards prolonged RFS time.

Statistical analyses were performed using electronic case report form (eCRF) data recorded until 12 months after the planned last treatment of the last patient, i.e., 36 months after start of treatment of last patient.

Efficacy endpoints were analyzed based on the intention-to-treat (ITT) population, including all randomized patients assigned to their respective treatment arm according to initial randomization.

The per-protocol (PP) population is the subset of patients in the ITT population who were compliant with the protocol and characterized by criteria such as:

- Measurement of the primary endpoint
- Absence of any major protocol violations (i.e. residual disease as assessed in medical review by a specialized CRO; residual metastases; metastases at baseline; metastases suspected before surgery but not confirmed by histology; primary cancer other than colorectal cancer; previous R2 resection; metastases other than hepatic metastases were resected; previous adjuvant chemotherapy; treatment with vaccine/placebo was discontinued prematurely without evidence of recurrence)
- Patients randomized in the wrong stratum.

The PP population was identified before unblinding the trial database and was also used for analyzing RFS time and 3-year OS rate; it was considered a secondary population.

The primary endpoints, RFS and OS, were evaluated using a Cox proportional hazards regression model, adjusted for the stratification factor resection status (R0 vs. R1). RFS and 3-year OS rate were described using Kaplan-Meier curves and associated summary statistics (e.g., median, 80% and 90% confidence intervals (CIs), and RFS and 3-year OS rate estimates).

Safety endpoints were assessed for all patients who were treated with at least 1 dose of study medication and for whom follow-up safety data has been documented (safety population). Safety results were summarized based on AEs, ISRs, vital signs and physical examinations and clinical laboratory assessments.

A total of 120 patients were planned to be accrued. The estimated median time to recurrence after primary resection of colorectal cancer liver metastases was estimated to be 10 months. Sample size was calculated aiming at a HR of 0.77 (increase of median time to recurrence to 13 months) based on an alpha-level of significance of 0.15 (2-sided), a lost to follow-up rate of 4% over 75 months. Accounting for a 2:1 randomization, 120 patients is were required in order to achieve a probability of 29.5% (3-year OS) and 40.3% (RFS) (power) to demonstrate the expected effect.

Follow-up ended 36 months after randomization of the last patient, i.e., approximately 75 months after initiation of the study).

Summary – Conclusions:

Patient characteristics:

The mean age was 60.0 years, ranging from 24 to 85 years. Overall, 80 (66.1%) patients were < 65 years of age and 41 (33.9%) were aged 65 to < 85 years. The greater proportion of patients (62.8%) were men. The mean BMI was 26.5, ranging from 18.3 to 57.7. Mean time since first diagnosis was 21.7 months. Most (76.9%) patients did not consume alcohol regularly; most (53.7%) had never smoked and a certain proportion (37.2%) had quit smoking. The proportion of ex-smokers was greater in the L-BLP25 arm compared with the placebo arm (45.6% vs. 21.4%), whereas the proportion of never-smokers was smaller (46.8% vs. 66.7%) (P = 0.0329). Apart from smoking status, the 2 treatment groups were well balanced with regard to demographic and other baseline characteristics.

The greater proportion (70.2%) of patients had ECOG performance status 0; the remaining patients

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(29.8%) with available data were ECOG performance status 1. Most patients had received previous systemic therapy (69.4%) or previous chemotherapy (68.6%), and a minority had previously been treated with previous immunotherapy (24.0%) or previous radiotherapy (20.7%). MUC1 staining was low in 13.2% of patients, moderate in 39.7% and strong in 26.4% of patients (not evaluable 19.8%, missing 1%).

The most frequent TNM parameters at first diagnosis were T3 (82 [67.8%] patients) – N1 (50 [41.3%] patients) – M1 (65 [53.7%] patients). The patients in the L-BLP25 arm, compared with the placebo arm, presented with less metastasized carcinomas in terms of M0-M1-MX staging (46.8%-46.8%-6.3% vs. 19.0%-66.7%-14.3%). The most frequent tumor grading was G2 (91 [75.2%] patients).

The rectum was the primary tumor site with the greatest proportion of patients affected (48 [39.7%] patients), followed by the descending colon (43 [35.5%] patients). There was an imbalance between treatment groups regarding tumor sites, with a larger proportion of patients in the L-BLP25 arm having the tumor in the rectum (43.0% vs. 33.3%) and a smaller proportion of patients in the L-BLP25 arm having the tumor in the descending colon (31.6% vs. 42.9%) compared to the placebo arm.

Most patients (104 [86.0%]) had less than 5 hepatic metastases resected, and their resection status most frequently was R0 (107 [88.4%]). Primary resectable tumors were more frequent than secondary (66.1% vs. 33.9%), and the proportion of patients with secondary resectability was somewhat higher in the L-BLP25 arm compared with the placebo arm (36.7% vs. 28.6%). A Fong score of 0 to 2 (low risk) was determined for 66.1% of patients in total (70.9% in the L-BLP25 arm and 57.1% in the placebo arm) and a score of 3 to 5 (high risk) for 33.9% of patients (29.1% in the L-BLP25 arm and 42.9% in the placebo arm), having more patients with high risk in the placebo arm.

Efficacy results:

Primary efficacy endpoint: The median RFS was 6.1 months (80% CI: 5.9, 8.8) for the L-BLP25 arm and 11.4 months (80% CI: 8.6, 19.8) for the placebo arm. The hazard ratio for RFS was 1.3 (90%CI: 0.9, 2.0). . The estimated 3-year OS rates were 69.1% and 79.1%. The global null hypothesis for the primary endpoint was tested using stratified log-rank test, 2 sided (OS, P = 0.2141; RFS, P = 0.1754). As the smaller P value (for RFS time) was not ≤ 0.1, the null hypothesis stating no differences between treatments in the probability of survival could not be rejected. Consequently, the null hypothesis related to RFS could not be rejected either. Overall, the primary endpoint was not reached.

Sensitivity analysis: When baseline factors including resection status, age, sex, MUC1 staining, prior systemic therapy, prior radiotherapy and time since first diagnosis were simultaneously entered in a Cox proportional hazards regression model of RFS, the factor resection status was the only factor with P value < 0.05 (HR = 2.70; P = 0.0051). For treatment the Wald test P value was 0.3540 (HR = 1.2).

Sensitivity analysis: When the above baseline factors were simultaneously entered in a Cox proportional hazards regression model of OS, For the factor age the lowest P Value was observed (P = 0.0838; HR = 1.028), followed by sex (P = 0.0899; HR [female] = 1.807).The effect of treatment was again not “significant” (P = 0.4253).

Further efficacy endpoint (median OS and 3-year RFS rate):The median OS was 62.8 months (80% CI: 45.8, 65.1) for L-BLP25 and was not estimable for the placebo arm. The estimated 3-year RFS rates were 20.8% and 31.5%, the estimated 3-year OS rates 69.1% and 79.1%, respectively. Hazard ratio for OS was 1.6 (90% CI: 0.9, 2.8).Secondary efficacy endpoint (RFS in patients with MUC1 positive cancer): Difference in RFS for the two study arms was evaluated using a Cox proportional hazards regression model, adjusted for the MUC1 staining. The 3 year RFS rate in the L-BLP25 arm was 36.4% for low MUC1 staining, 14.6% for moderate MUC1 staining, and 22.7% for strong MUC1 staining. The 3-year RFS rate in the placebo arm was 0.0% for low MUC1 staining, 20.8% for moderate MUC1 staining, and 44.4% for strong MUC1 staining. There were no “significant” differences between the RFS distributions (global likelihood ratio test of the multivariate model, P = 0.4760).

Secondary efficacy endpoint (OS in patients with MUC1 positive cancer): The 3-year OS rate in the L-BLP25 arm was 66.3% for low MUC1 staining, 78.7% for moderate MUC1 staining, and 74.7% for strong MUC1 staining. The 3-year OS rate in the placebo arm was 60.0% for low MUC1 staining, 83.0% for

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moderate MUC1 staining, and 85.7% for strong MUC1 staining. Differences in OS for the two study arms were evaluated using a Cox proportional hazards regression model, adjusted for the stratification factor MUC1 staining. There were no "significant" differences between the OS distributions (global likelihood ratio test, P = 0.6227).

Safety results:

Exposure:

Patients in the investigational arm received a mean (SD) single dose of 281.9 (39.0)mg/m^2 of CP, followed by a mean (SD) cumulative dose of 27.5 (12.7) mL of L-BLP25 (930ug of L-BLP25 had to be reconstituted in 2mL).

Adverse events and NCI-CTCAE toxicities:

The most common treatment-emergent adverse events (TEAEs) in both the L-BLP25 arm and the placebo arm included nausea (30.4%, 19.0%), fatigue (25.3%, 19.0%), diarrhea (21.5%, 21.4%), and viral upper respiratory tract infection (17.7%, 9.5%).

The grade 3 and 4 TEAEs most frequently recorded for the L-BLP25 arm were diarrhea, anemia, back pain, cholestatic jaundice (each grade 3, each in 2 patients), blood uric acid increased, and ileus (grade 3 and 4, each in 1 patient). None of the hematologic, renal or hepatic TEAEs were grade 4. Diarrhea and cholestasis (each grade 3, each in 2 patients) were the most frequent grade 3 TEAEs in the placebo arm.

The most common TEAEs assessed by the investigator as related to vaccination in the L-BLP25 arm were injection site erythema (8.9%), injection site reaction (6.3%), injection site swelling and fatigue (5.1% each). In the placebo arm, these were pruritus (9.5%), mechanical urticarial and injection site reaction (4.8% each).

Two deaths were reported as TEAEs. One patient treated with L-BLP25 died of Merkel cell carcinoma, which was suspected to be related to study drug by the investigator but rated as not suspected to be related to study drug by the sponsor considering that cancer patients are at an increased risk for secondary malignancies (Of note: a case of prostate cancer occurred in the placebo group). Another patient treated with L-BLP25 died of respiratory failure, considered not related to L-BLP25 by both the investigator and the sponsor.

Serious adverse events (SAEs) were reported for 23 (29.1%) and 14 (33.3%) patients in the L-BLP25 arm and placebo arm, respectively. The most frequently reported SAEs for L-BLP25 arm were ileus (3 [3.8%] patients), followed by general physical health deterioration, jaundice cholestatic, hypersensitivity, bronchitis and metastases to lung (2 [2.5%] patients each) as reported by the investigators. Most frequently reported for placebo was cholestasis (2 [4.8%] patients).

Among the SAEs reported for the L-BLP25 arm, the following events were considered by the investigator to be drug-related: injection site induration (1 event), tinnitus (2 events), large intestine perforation, peritonitis and neuroendocrine carcinoma of the skin (each in 1 [1.3%] patient). None of the SAEs in the placebo arm were assessed as drug-related.

ISRs of any form were recorded for 28 (23.1%) patients overall, 22 (27.8%) patients in the L-BLP25 arm and 6 (14.3%) patients in the placebo arm. Most ISRs were of mild intensity. There was one single case of a severe ISR: "injection site reaction" in the L-BLP25 arm, which resolved on the same day. None of the ISRs required discontinuation or interruption of vaccination or dose reduction.

TEAEs of special interest recorded in the L-BLP25 arm were grade 1 thrombocytopenia and grade 3 alkaline phosphatase increased, each in 2 (2.5%) patients. Except for grade 1 thrombocytopenia in 1 (1.3%) patient, none of those events in the L-BLP25 arm were assessed as related to study drug. TEAEs of special interest recorded in the placebo arm were grade 1 and grade 2 thrombocytopenia, each in 1 patient, grade 2 alkaline phosphatase increased in 1 patient, and grade 3 AST increased in 1 patient. None of those events were considered to be related to study drug.

Other observations related to safety:

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The most frequent clinically relevant abnormal abnormalities in the L-BLP25 and placebo arm at the EOT evaluation were carcinoembryonic antigen (CEA) in 39% and 47% of patients (screening: 14% each), lactate dehydrogenase (LDH) 23% and 22% (screening: 16% and 14%), cancer antigen 19-9 (CA 19-9) 19% and 8% (screening: 6% and 0%), INR 18% and 19% (screening: 21% and 12%), neutrophils 16% and 31% (screening: 12% and 24%), urea 15% and 6% (screening: 8% and 10%), and PTT 11% and 14% (screening: 10% and 21%), respectively. There was no clear difference between treatment groups regarding the proportion of patients with clinically relevant laboratory abnormalities. No significant hematologic toxicity was observed during treatment with L-BLP25.

There was no indication of a clinically relevant difference between treatments regarding blood pressure, pulse, body temperature or respiratory rate.

Conclusions:

The LICC trial failed to meet its primary endpoint of significantly improving RFS and OS with L-BLP25. In the L-BLP25 and placebo arms, the estimated 3-year OS rates were 69.1% and 79.1%, and the estimated 3-year RFS rates were 20.8% and 31.5%, respectively. MUC1 expression was not associated with outcome.

No clinically significant hematologic toxicity was observed during treatment with L-BLP25. One patient treated with L-BLP25 died of Merkel cell carcinoma, which was assessed as being related to L-BLP25 by the investigator but rated as not suspected to be related to study drug by the sponsor. Apart from this, the safety profile in this study was consistent with the data in the Reference Safety Information. More than a quarter (28%) of patients vaccinated with L-BLP25 had injection site reactions, in most cases mild, and none requiring discontinuation/interruption of vaccination or dose reduction.

Nevertheless, when comparing survival times of the LICC study with studies with a comparable patient collective, LICC shows strikingly good survival times that might be by part but not altogether explained by the young patient collective in LICC.

Date of report: 29-NOV-2018 (final)

Protocol/ Amendment	Type of Amendment	Changes Implemented	Protocol Version/ Date	Favorable opinion of the leading ethics committee (Date)	Approval of the relevant competent authority (Date)
Initial Submission					
Germany	Initial submission	N/A	Version 1.0 10.05.2011 Version 2.0, 18.08.2011	27.09.11	05.09.11
Austria	Initial submission	N/A	Version 1.0, 05.07.2011 Version 2.0, 18.08.11 Version 3.0, Nov 11	05.01.12	27.07.11
Belgium	Initial submission	N/A	Version 3.0 Nov 11	05.10.2012	14.06.12
Amendment I					
Germany	Substantial, Amendment PIC (update of no. of subjects and inclusion of detection of lymphoma in rats) and Study protocol (addition of monthly pregnancy test in Austria)	Amendment to study protocol, IB Version 6.0	Version 3.0, Nov 11	11.01.12	25.01.12
Austria	substantial	Amendment to study protocol	Version 4.0, 12.07.12	20.09.12	05.09.12 (confirmation of receipt)
Belgium	substantial	Amendment to study protocol	Version 4.0, 12.07.12	N/A	23.11.12
Amendment II					
Germany	Substantial, Extension of time from resection to inclusion into study from 6 weeks to 8 weeks	Amendment to study protocol	Version 4.0, 12.07.12	26.09.12	04.10.12
Austria	Substantial, IB Version 7	Update of IB	No change	24.01.13	Silent approval
Belgium	substantial	N/A	N/A	N/A	N/A

Amendment III					
Germany	Substantial, Reduction of treatment period from 3 years to 2 years, change of endpoints, change of reporting period of adverse events, extension of recruitment period, amendment of handling medication after reconstitution, change in inclusion criteria regarding coagulation	Amendment to study protocol, Update of IB Version 9.0	Version 5.0, 12.12.14	03.03.15	21.01.15
Austria	substantial	Amendment to study protocol, Update of IB Version 9.0	Version 5.0 12.12.14	30.01.15	Silent approval
Belgium	substantial	N/A	N/A	N/A	N/A

	Center (Name)	Department	Zip Code	City / District	Country	Number of Patients
1	Universitätsmedizin der Johannes Gutenberg-Universität; Langenbeckstr.1	I. Medizinische Klinik	55131	Mainz	Deutschland	17
2	Universitätsklinikum Frankfurt; Theodor-Stern-Kai 7	Klinik f. Allgemein- & Viszeralchirurgie	60590	Frankfurt a.M.	Deutschland	6
3	Klinikum der Universität München; Marchioninistr. 15	Medizinische Klinik III	81377	München	Deutschland	4
4	Kliniken Nordoberpfalz AG ; Söllnerstr. 16	Medizinische Klinik I	92637	Weiden i.d.O.	Deutschland	6
5	Städtisches Klinikum Karlsruhe gGmbH; Moltkestr. 90	Allgemein- und Visceralchirurgie	76133	Karlsruhe	Deutschland	2
6	Universitätsklinikum Essen (AöR); Hufelandstr. 55	Klinik f. Innere Medizin/ Tumorforschung	45147	Essen	Deutschland	24
7	Universitätsklinikum Ulm; Albert-Einstein-Allee 23	Klinik für Innere Medizin I	89081	Ulm	Deutschland	0
8	Robert-Bosch-Krankenhaus; Auerbachstr. 110	Innere Medizin	70376	Stuttgart	Deutschland	4
9	Charité Campus Virchow-Klinikum; Augustenburger Platz 1	Allgem.-Visceral- u.Transplant.chirurgie	13353	Berlin	Deutschland	4

10	Praxis für Hämatologie und Onkologie	Onkologie/Hämatologie	202XX	Hamburg	Deutschland	14
11	Klinikum Dortmund gGmbH; Beurhausstr. 110	Med. Klinik Mitte, Gastro/Häma/Onko/Endo	44137	Dortmund	Deutschland	0
12	Praxis für Onkologie	Innere Medizin	112XX	Dresden	Deutschland	1
13	Gemeinschaftspraxis für Hämatologie und Onkologie		776XX	Landkreis Ortenaukreis	Deutschland	3
14	Praxis für Hämatologie und Onkologie		454XX	Regierungsbezirk Düsseldorf	Deutschland	9
15	Praxis für Hämatologie und Onkologie		456XX	Regierungsbezirk Münster	Deutschland	9
16	Leopoldina-Krankenhaus; Gustav-Adolf-Str. 8	Innere Medizin	97422	Schweinfurt	Deutschland	0
17	Klinikum Esslingen GmbH; Hirschlandstr. 97	Innere Medizin, Onkologie	73730	Esslingen a.N.	Deutschland	4
18	Klinikum Altenburger Land GmbH; Am Waldessaum 10	Klinik für Hämatologie und Onkologie	4600	Altenburg	Deutschland	3
19	Krankenhaus der Barmherzigen Brüder; Nordallee 1	Allgemein- & Viszeralchirurgie	54292	Trier	Deutschland	2
20	Universitätsklinikum Leipzig; Liebigstraße 20	Universitäres Krebszentrum (UCCL)	4103	Leipzig	Deutschland	4

21	Universitätsklinikum Magdeburg A. ö. R.; Leipziger Str. 44	Allgemein-, Viszeral- und Gefäßchirugie	39120	Magdeburg	Deutschland	2
22	Klinikum Darmstadt GmbH ; Grafenstr. 9	Med. Klinik V - Onkologie & Hämatologie	64283	Darmstadt	Deutschland	3
23	Universitätsklinikum Regensburg; Franz-Josef-Strauß-Allee 11		93053	Regensburg	Deutschland	1
24	Universitätsklinikum Gießen und Marburg GmbH; Baldingerstr.	Hämatologie/Onkologie/Immunologie	35043	Marburg	Deutschland	1
25	LKH Salzburg; Müllner Hauptstr. 48	Innere Medizin III, SCRI-CCCIT gGmbH	5020	Salzburg	Österreich	2
26	LKH_Univ. Klinikum Graz; Auenbrugger Platz 15	Innere Medizin - Onkologie	8036	Graz	Österreich	0
27	Antwerp Hospital; Wilrijkstraat 10	Department of Oncology	2650	Edegem	Belgien	0
28	University Hospital Gasthuisberg ; Herestraat 49	Digesttive Oncology Unit	3000	Leuven	Belgien	0