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Adjuvant MUC vaccination with tecemotide after resection of colorectal liver metastases: a randomized, double-blind, placebo-controlled, multicenter AIO phase II trial (LICC)

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ABSTRACT

Resection of colorectal liver metastases (CRLM) is a potential curative treatment for patients with metastatic colorectal cancer (mCRC) with liver-limited disease (LLD). Although long-term survival improved considerably within the last decades, high recurrence rates of 50-75% after resection remain a major challenge.Tecemotide (L-BLP25) is an antigen-specific cancer vaccine inducing immunity against mucin-1 (MUC1). The LICC trial aimed to improve survival in patients with mCRC after R0/R1 resection of CRLM. LICC was a binational, randomized, double-blind, placebo-controlled, multicenter phase 2 study including patients with R0/R1 resected CRLM without evidence of metastatic disease outside the liver. Co-primary endpoints were recurrence-free survival (RFS) and 3-year overall survival (OS) rate, secondary endpoints were RFS and OS in subgroups with different MUC1 expression and safety. In total, 121 patients were 2:1 randomized between Oct 2011 and Dec 2014to receive tecemotide (N=79) or placebo (N=42). Baseline characteristics were well balanced. Median RFS was 6.1 months (95% CI 4.5-8.9) and 11.4 months (95% CI 3.7-21.2) (P = .1754), 3-year OS rate 69.1% and 79.1%, median OS 62.8 months and not reached in the tecemotide vs. placebo arm (P = .2141), respectively. Cox regression models revealed no dependence of RFS or OS on MUC1 expression. The most common tecemotide-related grade 3/4 adverse events were diarrhea, injection site reaction, intestinal perforation, peritonitis and tinnitus (1.3% each). The LICC trial failed to meet its primary endpoints of significantly improving RFS and OS with tecemotide. However, both arms showed unexpectedly long OS. MUC1 expression was not associated with outcome.

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Abbreviations: AE: adverse event; CP: cyclophosphamide; CRC: colorectal cancer; CT: computed tomography; ECOG: Eastern Cooperative Oncology Group; FU: follow-up; HR: hazard ratio; IHC: immunohistochemical staining; ITT: intention-to-treat; DSMB: Data Safety Monitoring Board; LLD: liver-limited disease; mCRC: metastatic colorectal cancer; MPLA: monophosphoryl lipid; AMRI: magnetic resonance imaging; MUC1: mucin 1; NA: not applicable; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NS: normal saline; NSCLC: non-small-cell lung carcinoma; OS: overall surviva; IPP: per protocol; RAS: Rat sarcoma; RFS: recurrence-free survival; TEAE: treatment-emergent adverse event; UICC: Union for International Cancer Control; US: ultrasound; vs.: versus.

Introduction

Patients with metastatic colorectal cancer (mCRC) and liver-limited disease (LLD) have a chance of long-term survival and cure after resection of colorectal liver metastases (CRLM).[1–3] However, high recurrence rates of >50% after resection remain

a major challenge.[4] Five-year survival rates range between 28%–58%,[4–11] median overall survival (OS) between 46 and 62 months.[10–13]

The potential benefit of chemotherapy before and/or after surgery was studied in two large trials in patients with primary resectable CRLM, the EORTC Intergroup trial 40983 reported by Nordlinger et al.[10,14] and the FFCD ACHBTH AURC 9002 trial reported by Portier et al.[11] Peri- and postoperative chemotherapy had a beneficial effect on RFS compared to surgery alone (20.0 vs. 12.5 months[10] and 24.4 vs. 17.6 months[11]). Though observed differences in OS were not statistically significant (61.3 vs. 54.3 months[10] and 62.1 vs. 46.4 months[11]) they may be of clinical relevance. Patients with primarily unresectable CRLM in the CELIM trial[12,15] and a subgroup analysis of the FIRE-3 trial with LLD and metastasectomy showed survival times of 53.9 months[12] and 56.2 months,[13] respectively.

Tecemotide is an antigen-specific cancer vaccine inducing immunity against mucin-1 (MUC1), a glycoprotein expressed on the cell surface of many normal epithelial tissues and over- or aberrantly expressed on many carcinoma cells, including primary CRC[16] and CRLM.[17] MUC1 is known to promote tumor cell growth, survival, and metastasis.[18,19] Tecemotide incorporates the synthetic, 25 amino acid, non-glycosylated MUC1 lipopeptide (BLP25), and the nonspecific immunoadjuvant monophosphoryl lipid A (MPLA) in a liposomal delivery system.[18] Its proposed mode of action is to trigger an antigen-specific T-cell immune response in tumor cells expressing the MUC1 antigen.[18] In patients with non-small-cell-lung carcinoma (NSCLC), tecemotide has shown promising results for subgroups but lacked statistically significant survival difference in the total population.[20,21]

The LICC trial (LICC: **L**-BLP25 **I**n **C**olorectal **C**ancer) was designed to compare the efficacy and safety of adjuvant tecemotide versus placebo in patients with resected CRLM.[22]

Patients and methods

Study design and patient population

LICC was a randomized, placebo-controlled, multicenter, binational, double-blind phase II trial (registered on ClinicalTrials.gov No. NCT01462513). Patients were 2:1 randomized to tecemotide or placebo and stratified by resection status (R0/R1).[22] Patients with histologically confirmed adenocarcinoma of the colon or rectum and stage IV mCRC and LLD, aged ≥18 years, with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ function were included after R0/R1 resection of primary tumor and liver metastases with curative intent within the last 8 weeks before randomization. Key exclusion criteria were metastases other than liver metastases, R2 and Rx hepatic metastasectomy, chemotherapy, and/or immunotherapy within 4 weeks prior to randomization and any known autoimmune disease or immunodeficiency. No evidence of disease after resection of CRLM had to be confirmed in a baseline computed tomography (CT) or magnetic resonance imaging (MRI) scan before randomization.

The study was conducted in accordance with Good Clinical Practice and in accordance with the ethical standards of the national research committee and the 1964 Declaration of Helsinki and its later amendments. The study protocol was approved by the Institutional Review Board at the participating sites and the ethic committee of the Landesärztekammer Rheinland-Pfalz, Germany. All patients provided written informed consent to participate. A Data Safety Monitoring Board (DSMB) held periodic monitoring to ensure subject safety and data validity.

Treatment

For an immune modulation effect, cyclophosphamide (300 mg/m2) (CP) was given intravenously 3 days prior to the first tecemotide dose. The placebo group received a single dose of saline solution (NS) before the subcutaneous administration of placebo. Patients received subcutaneous tecemotide (930 µg) or placebo once weekly for 8 consecutive weeks during the primary treatment phase, followed by a maintenance treatment phase with vaccinations at 6-week intervals for 2 years. A planned total period of 3 years close surveillance and maintenance treatment with 12-week intervals in year 3 was shortened to 2 years (amendment in 2014) due to the development stop of tecemotide and thus limited shelf life of remaining stocks. Maintenance treatment lasted until recurrence or until 2 years after randomization at most. Follow-up (FU) for all patients ended 3 years after the last patient was randomized into the study.

Efficacy and safety assessment

Disease recurrence was followed by CT or MRI (RECIST v 1.1), alternating with ultrasound (US) imaging of the liver performed at six-week intervals during the maintenance treatment phase for two years, starting six weeks after the end of the primary treatment phase. Standard safety assessments were performed during the study, including assessment of adverse events (AEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCAE v.3.0), laboratory parameters, and physical examinations. Treatment-emergent adverse events (TEAEs) of special interest were thrombocytopenia, hepatic dysfunction, and autoimmune disease. TEAEs were assessed and causality was graded as related or not related to the study drug as determined by the investigator. AEs and SAEs suspected to be related to the investigational medicinal product had to be recorded until 12 weeks after the last treatment or during the whole FU period, respectively. Unrelated TEAEs were recorded until 42 days after the last treatment. For further details see Schimanski et al. 2012.[22]

Biomarkers

Ninety-six of 121 paraffin-embedded tissue blocks were available for immunohistochemical staining (IHC) of MUC1. The IHC was done as previously described,[23] slides were incubated with the primary antibody for MUC1 (214D4, Millipore, 1:100) according to the manufacturer's instruction. The staining was evaluated by two independent, blinded investigators according to Remmele's Immunoreactive Score (see supplement 1).[24]

Statistical analysis

For sample size calculations, the assumed hazard ratio (HR) for RFS was 0.77, corresponding to an increase of 3 months from 10

to 13 months median time to recurrence under tecemotide, with a one-sided alpha of 0.075 (corresponding to a two-sided alpha of 0.15) per test and a total loss to FU rate of 4%. As there were two primary endpoints, adjusting for multiple testing was done using the Bonferroni-Holm procedure. Therefore, in order to keep the overall significance level of 0.15 one-sided, the smaller p-value of the two has to be below 0.075 (one-sided). Considering a 2:1 randomization, 120 patients allowed to achieve a power of 30.7% (3-year OS) and 44.5% (RFS). Notably, the phase II trial LICC was not designed for confirmatory purpose but aimed to explore potential trends of efficacy in the studied population.

The primary analysis population for all efficacy endpoints was the intention-to-treat (ITT) population comprising all randomized patients, according to the treatment assignment. Safety was analyzed for all patients receiving at least one dose of study medication. Co-primary endpoints were recurrence-free survival (RFS) and 3-year OS rate. Secondary endpoints were safety and tolerability as well as RFS and OS in subgroups with low, medium, and high MUC1 expression. MUC1 expression on tumor tissues was analyzed to discover a potential association with progression and survival and to test whether MUC1 is predictive of tecemotide benefit. RFS, based on RECIST v.1.1, was calculated as the period between randomization and date of disease recurrence as determined via standard imaging or death. OS was calculated from the date of randomization until the date of death. Kaplan-Meier estimates were used for the analysis of RFS and OS. Stratified log-rank tests (2-sided, family-wise error rate alpha = 30%, applying the Bonferroni-Holm procedure for multiple testing) were carried out for analysis of RFS and OS, with resection status (R0 vs. R1+ R2+ RX) as stratification factor. For RFS, patients who were lost to follow-up (FU) or who had withdrawn from the study were censored at the last time of recurrence evaluation. For OS, patients lost to FU or who

had withdrawn from study were censored at the time of last contact or time of withdrawal. Sensitivity analyses on efficacy endpoints were conducted including per-protocol (PP) analysis and Cox proportional hazards regression models that were applied to the ITT population to test for potential differences in OS and RFS as a function of treatment and one of the variables resection status, age, sex, MUC1 staining, prior systemic therapy, prior radiotherapy, time since the first diagnosis, Fong Score, grading, number of resected metastases or resectability. Statistical analysis was performed with SAS 9.4 TS1 M5.

Results

Patient characteristics

Between Oct 2011 and Dec 2014, 121 patients were randomized at 22 study sites in Germany and Austria to receive either tecemotide (n = 79, 65.3%) or placebo (n = 42, 34.7%) Figure 1. For 12 patients (n = 10 tecemotide arm, n = 2 placebo arm), resection with curative intent was performed more than 56 days (range 58–100 days) before randomization. A centralized radiologic review led to the exclusion of 11 patients (n = 7 tecemotide arm, n = 4 placebo arm) with residual disease at baseline from the PP population. Baseline characteristics (Table 1) were generally balanced between treatment arms except for ECOG status (more patients in the tecemotide arm had ECOG 0, P = .0357). Non-significant differences were found for UICC stage, M0/M1 status, primary tumor site, Fong score, and resection status.

Efficacy

Kaplan-Meier analyses for RFS and OS are shown in Figure 2. Median RFS was 8.6 months (95% CI, 5.9–11.4), 6.1 months (95% CI, 4.5–8.9) and 11.4 months (95% CI, 3.7–21.2) in the
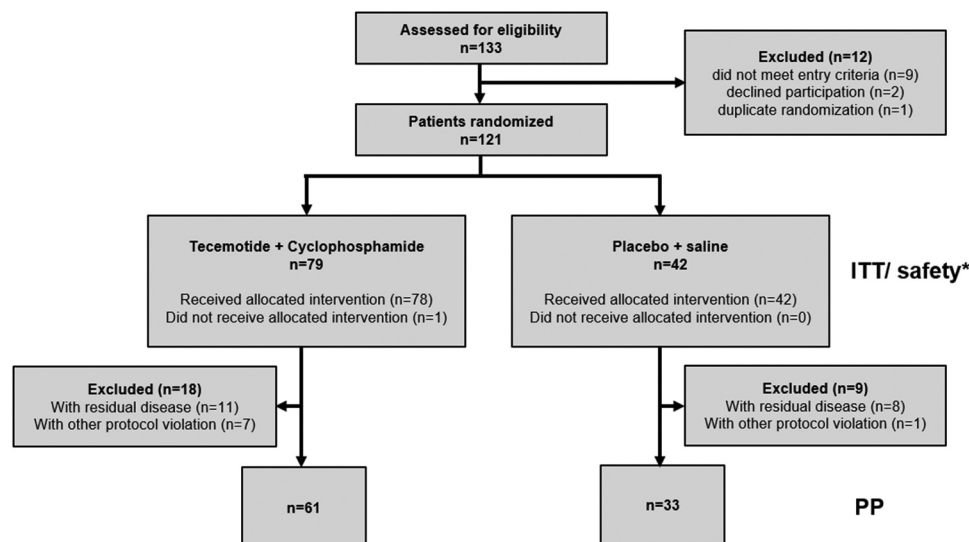

Figure 1. CONSORT flow diagram of the LICC trial. * One patient in the tecemotide arm did not receive vaccination but received CP and was included in the ITT and safety population. In the tecemotide arm, one patient had one R2 resected metastasis besides R0 resected metastases and one patient had one RX metastasis besides R0 and R1 resected metastases. These patients were allocated to the "Non-R0" subgroup in the ITT population and were excluded from the PP population. A centralized radiologic review was conducted for 80 patients, which led to the exclusion of 11 patients (n = 7 tecemotide arm, n = 4 placebo arm) with residual disease at baseline from the per-protocol (PP) population. Abbreviations: ITT: intention-to-treat population, PP: per-protocol population.

Table 1. Patient and tumor characteristics at baseline (ITT population).

		Tecemotide (n = 79)	Placebo (n = 42)	All patients (n = 121)	P-value
Age at start of therapy, years [Median (range)]	-	60.0 (24–84)	58.5 (30–85)	60.0 (24–85)	0.5137 [b]
Sex [n (%)]	Female	30 (38.0)	15 (35.7)	45 (37.2)	
	Male	49 (62.0)	27 (64.3)	76 (62.8)	0.8456 [c]
Comorbidity [a] [n (%)]	No	13 (16.5)	6 (14.3)	19 (15.7)	
	yes	66 (83.5)	36 (85.7)	102 (84.3)	1.0000 [c]
ECOG performance status [a] [n (%)]	0	61 (77.2)	24 (57.1)	85 (70.2)	
	1	18 (22.8)	18 (42.9)	36 (29.8)	0.0357 [c]
Fong score	0	9 (11.4)	4 (9.5)	13 (10.7)	
	1	19 (24.1)	12 (28.6)	31 (25.6)	
	2	28 (35.4)	8 (19.0)	36 (29.8)	
	3	16 (20.3)	11 (26.2)	27 (22.3)	
	4	7 (8.9)	6 (14.3)	13 (10.7)	
	5	0 (0)	1 (2.4)	1 (0.8)	0.2971 [c]
Time since primary diagnosis, months [Median (range)]	-	20 (1.4–121.3)	12.6 (0.9–73.6)	18.3 (0.9–121.3)	0.1247 [d]
Previous chemotherapy [n (%)]	No	24 (30.4)	14 (33.3)	38 (31.4)	
	Yes	55 (69.6)	28 (66.7)	83 (68.6)	0.8375 [c]
Previous immunotherapy [n (%)]	No	58 (73.4)	34 (81.0)	92 (76.0)	
	Yes	21 (26.6)	8 (19.0)	29 (24.0)	0.3825 [c]
Primary tumor site [n (%)]	Colon				
	ascending	7 (8.9)	5 (11.9)	12 (9.9)	
	descending	25 (31.6)	18 (42.9)	43 (35.5)	
	multiple sites	1 (1.3)	0 (0)	1 (0.8)	
	transversum	3 (3.8)	2 (4.8)	5 (4.1)	
	unknown	9 (11.4)	3 (7.1)	12 (9.9)	
	Rectum	34 (43.0)	14 (33.3)	48 (39.7)	0.3339 [c]
Tumor grading at primary diagnosis [n, %]	G1	1 (1.3)	1 (2.4)	2 (1.7)	
	G2	61 (77.2)	30 (71.4)	91 (75.2)	
	G3	11 (13.9)	9 (21.4)	20 (16.5)	
	G4	0 (0)	1 (2.4)	1 (0.8)	
	GX	6 (7.6)	2 (4.8)	7 (5.8)	0.3134 [c]
UICC stage at primary diagnosis	I	3 (3.8)	0 (0)	3 (2.5)	
	II	9 (11.4)	2 (4.8)	11 (9.1)	
	III	25 (31.6)	6 (14.3)	31 (25.6)	
	IV	37 (46.8)	28 (66.7)	65 (53.7)	
	unknown	5 (6.3)	6 (14.3)	11 (9.1)	0.0457 [c]
Resectability [n, %]	Primary	50 (63.3)	30 (71.4)	80 (66.1)	
	Secondary	29 (36.7)	12 (28.6)	41 (33.9)	0.4234 [c]
Number of resected metastases [n, %]	<5	70 (88.6)	34 (81.0)	104 (86.0)	
	5–10	8 (10.1)	6 (14.3)	14 (11.6)	
	>10	1 (1.3)	2 (4.8)	3 (2.5)	0.3324 [c]
Resection status [n, %]	R0	69 (87.3)	38 (90.5)	107 (88.4)	
	R1	9 (11.4)	4 (9.5)	13 (10.7)	
	R2	1 (1.3)	0 (0)	1 (0.8)	0.7687 [c]
MUC1 staining [n (%)]	Low	11 (13.9)	5 (11.9)	16 (13.2)	
	Moderate	30 (38.0)	18 (42.9)	48 (39.7)	
	Strong	22 (27.8)	10 (23.8)	32 (26.4)	
	Not evaluable	16 (20.3)	8 (19.0)	24 (19.8)	
	Missing	0 (0)	1 (2.4)	1 (0.8)	0.9419 [c]

[a] at enrollment; [b] two sample t-test (two-sided); [c] exact Fisher test (two-sided); [d] Wilcoxon test (two-sided) **Abbreviations**: ECOG: Eastern Cooperative Oncology Group; UICC: Union for international cancer control

total ITT population, tecemotide and placebo arm, respectively. The global null hypothesis for RFS was not rejected (P = .1754). The 3-year RFS rates were 24.5% (95% CI, 17.2–32.6), 20.8% (95% CI, 12.6–30.5) and 31.5% (95% CI, 18.1–45.9) for the total population, tecemotide and placebo, respectively.

Median OS was 65.1 months (95% CI 45.9-NA) in the total ITT population, 62.8 months (95% CI, 43.0-n.e.) in the tecemotide arm and not yet reached in the placebo arm at the time of analysis. There was no significant difference in OS between treatment arms (P = .2141). The estimated 3-year OS rate was 73% (95% CI, 63.2–80.5), 69.1% (95% CI, 56.1–78.9) and 79.1%

(95% CI, 62.5–89.0) for the total population, tecemotide and placebo, respectively.

PP analysis revealed no between-arm differences with respect to RFS and OS according to stratified log-rank tests with stratification factor resection (OS: P = .1004, two-sided; RFS: P = .0741, two-sided) (Supplement 2). Cox proportional hazards regression models revealed no significant effect of treatment on RFS or OS neither with nor without adjusting for potential exploratory variables (Supplement 3). The variables number of resected metastases and resection status showed the most pronounced effect on RFS in multivariate
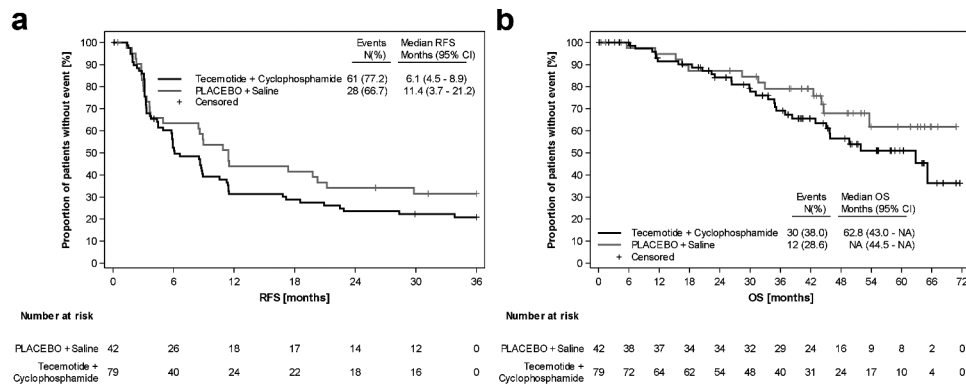
Figure 2. Kaplan-Meier analyses of the ITT population. A) Recurrence-free survival. B) Overall survival.

models, with HRs of 2.85 (>5 vs ≤5) and 2.52 (R1 vs R0) and *P* values of 0.0026 (≥5 vs <5) and 0.0048 (R1 vs R0) respectively (Supplement 4).

Subgroups according to MUC1 expression levels (low, medium, high) were analyzed for RFS and OS for both treatment arms (Figure 3). Cox proportional hazards regression with MUC1 and treatment as covariates revealed neither significant differences between treatment arms (ITT) nor between different levels of MUC1 staining regarding RFS and OS. Also, for the PP
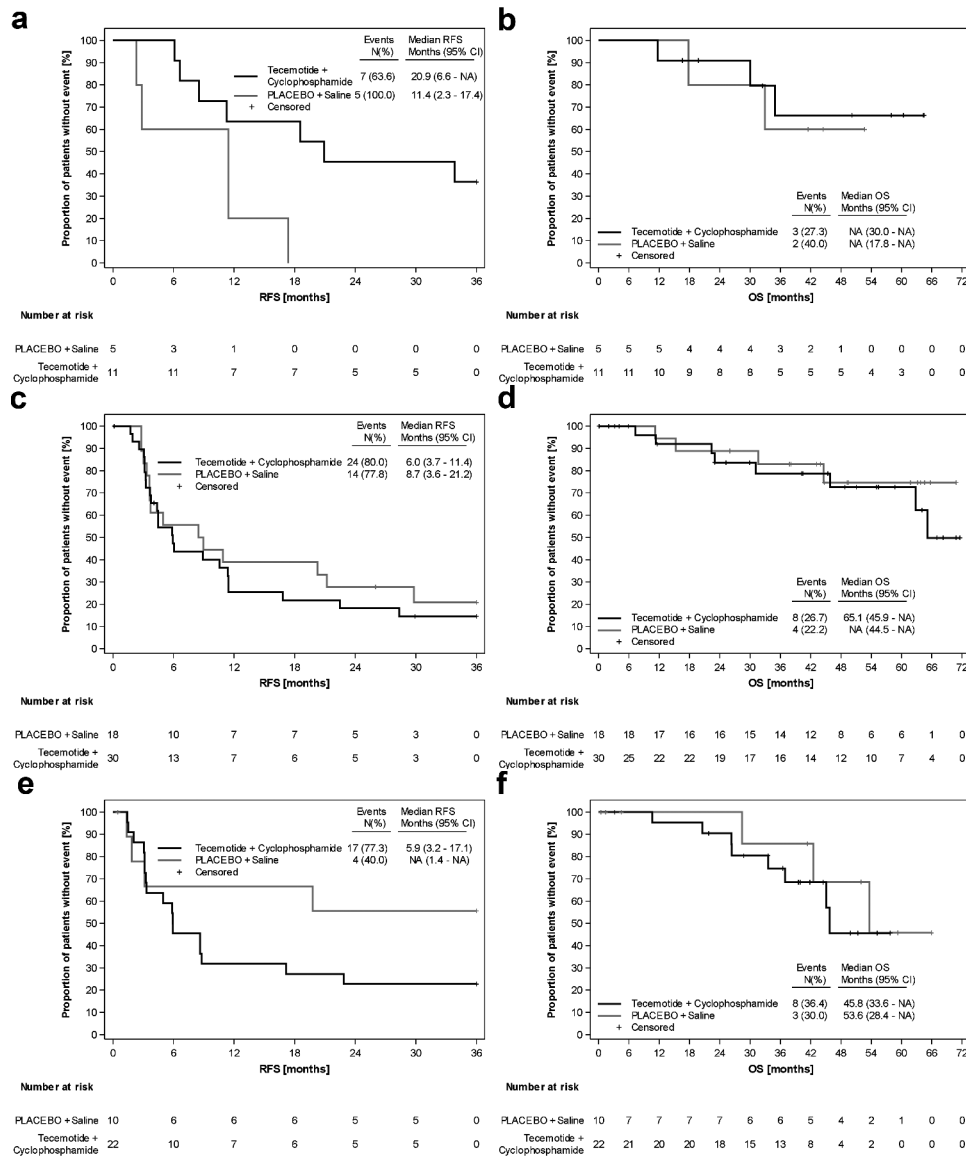

Figure 3. Kaplan-Meier analyses of the ITT population, according to MUC1 expression. A) RFS MUC1 low B) OS MUC1 low C) RFS MUC1 medium D) OS MUC1 medium E) RFS MUC1 high F) OS MUC1 high.
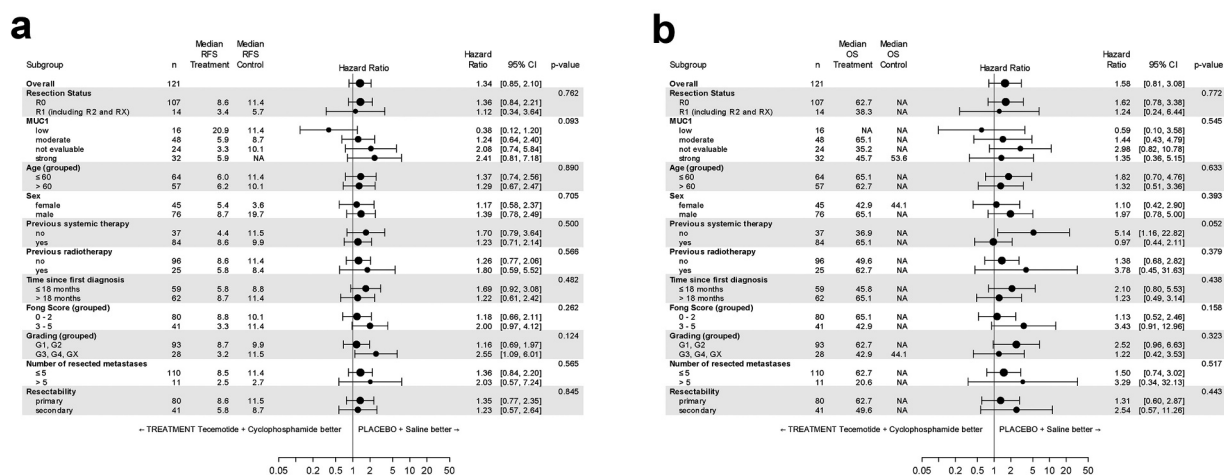
a

Subgroup	n	Median RFS Treatment	Median RFS Control	Hazard Ratio	95% CI	p-value
Overall	121			1.34	[0.85, 2.10]	
Resection Status						0.762
R0	107	8.6	11.4	1.36	[0.84, 2.21]	
R1 (including R2 and RX)	14	3.4	5.7	1.12	[0.34, 3.64]	
MUC1						0.093
low	16	20.9	11.4	0.38	[0.12, 1.20]	
moderate	48	5.9	8.7	1.24	[0.64, 2.40]	
not evaluable	24	3.3	10.1	2.08	[0.74, 5.84]	
strong	32	5.9	NA	2.41	[0.81, 7.18]	
Age (grouped)						0.890
≤ 60	64	6.0	11.4	1.37	[0.74, 2.56]	
> 60	57	6.2	10.1	1.29	[0.67, 2.47]	
Sex						0.705
female	45	5.4	3.6	1.17	[0.58, 2.37]	
male	76	8.7	19.7	1.39	[0.78, 2.49]	
Previous systemic therapy						0.500
no	37	4.4	11.5	1.70	[0.79, 3.64]	
yes	84	8.6	9.9	1.23	[0.71, 2.14]	
Previous radiotherapy						0.566
no	96	8.6	11.4	1.26	[0.77, 2.06]	
yes	25	5.8	8.4	1.80	[0.59, 5.52]	
Time since first diagnosis						0.482
≤ 18 months	59	5.8	8.8	1.69	[0.92, 3.08]	
> 18 months	62	8.7	11.4	1.22	[0.61, 2.42]	
Fong Score (grouped)						0.262
0 - 2	80	8.8	10.1	1.18	[0.66, 2.11]	
3 - 5	41	3.3	11.4	2.00	[0.97, 4.12]	
Grading (grouped)						0.124
G1, G2	93	8.7	9.9	1.16	[0.89, 1.97]	
G3, G4, GX	28	3.2	11.5	2.55	[1.09, 6.01]	
Number of resected metastases						0.565
≤ 5	110	8.5	11.4	1.36	[0.84, 2.20]	
> 5	11	2.5	2.7	2.03	[0.57, 7.24]	
Resectability						0.845
primary	80	8.6	11.5	1.35	[0.77, 2.35]	
secondary	41	5.8	8.7	1.23	[0.57, 2.64]	

← TREATMENT Tecemotide + Cyclophosphamide better   PLACEBO + Saline better →

0.05 0.2 0.5 1 2 5 10 20 50

b

Subgroup	n	Median OS Treatment	Median OS Control	Hazard Ratio	95% CI	p-value
Overall	121			1.58	[0.81, 3.08]	
Resection Status						0.772
R0	107	62.7	NA	1.62	[0.78, 3.38]	
R1 (including R2 and RX)	14	38.3	NA	1.24	[0.24, 6.44]	
MUC1						0.545
low	16	NA	NA	0.59	[0.10, 3.58]	
moderate	48	65.1	NA	1.44	[0.43, 4.79]	
not evaluable	24	35.2	NA	2.98	[0.82, 10.78]	
strong	32	45.7	53.6	1.35	[0.36, 5.15]	
Age (grouped)						0.633
≤ 60	64	65.1	NA	1.82	[0.70, 4.76]	
> 60	57	62.7	NA	1.32	[0.51, 3.36]	
Sex						0.393
female	45	42.9	44.1	1.10	[0.42, 2.90]	
male	76	65.1	NA	1.97	[0.78, 5.00]	
Previous systemic therapy						0.052
no	37	36.9	NA	5.14	[1.16, 22.82]	
yes	84	65.1	NA	0.97	[0.44, 2.11]	
Previous radiotherapy						0.379
no	96	49.6	NA	1.38	[0.68, 2.82]	
yes	25	62.7	NA	3.78	[0.45, 31.63]	
Time since first diagnosis						0.438
≤ 18 months	59	45.8	NA	2.10	[0.80, 5.53]	
> 18 months	62	65.1	NA	1.23	[0.49, 3.14]	
Fong Score (grouped)						0.158
0 - 2	80	65.1	NA	1.13	[0.52, 2.46]	
3 - 5	41	42.9	NA	3.43	[0.91, 12.96]	
Grading (grouped)						0.323
G1, G2	93	62.7	NA	2.52	[0.96, 6.63]	
G3, G4, GX	28	42.9	44.1	1.22	[0.42, 3.53]	
Number of resected metastases						0.517
≤ 5	110	62.7	NA	1.50	[0.74, 3.02]	
> 5	11	20.6	NA	3.29	[0.34, 32.13]	
Resectability						0.443
primary	80	62.7	NA	1.31	[0.60, 2.87]	
secondary	41	49.6	NA	2.54	[0.57, 11.26]	

← TREATMENT Tecemotide + Cyclophosphamide better   PLACEBO + Saline better →

0.05 0.2 0.5 1 2 5 10 20 50

Figure 4. Forest Plots for the ITT population. A) Recurrence-free survival and B) Overall survival. *P*-values are for testing interaction of treatment with subgroup, thus describing difference in treatment effects across subgroups.

population no significant differences were observed (Supplement 5). Subgroup analyses for RFS and OS are presented in Figure 4.

Safety

Median vaccination durations were 25 weeks and 49 weeks in the tecemotide and placebo arm, respectively. The corresponding median number of vaccinations was 11 (range 3–27) and 15 (range 2–27). Median FU was 40.1 months (tecemotide arm: 36.5 months, placebo arm: 43.6 months).

An overview of TEAEs can be found in Table 2. TEAEs were recorded for 90.1% of patients (87.3% tecemotide arm, 95.2% placebo arm). Most events were of grade 1/2. Grade 3/4 events were reported for 28.1% of patients (29.1% tecemotide arm, 26.2% placebo arm). The most common TEAEs in the tecemotide and the placebo arm were nausea (27.8%, 19.0%), injection site reaction (29.1%, 14.3%), fatigue (22.8%, 19.0%), diarrhea (17.7%, 16.7%), viral upper respiratory tract infection (17.7%, 9.5%), and abdominal pain (10.1%, 16.7%), respectively. Most frequent grade 3/4 TEAEs were diarrhea, anemia, back pain, injection site reaction, and blood uric acid increased (2 events each, 2.5%) in the tecemotide arm and diarrhea and cholestasis (2 events each, 4.8%) in the placebo arm Table 3. For more details see supplement 6.

TEAEs considered by the investigator as possibly related to study treatment (tecemotide+CP or placebo+NS) occurred in

Table 2. Overview of treatment-emergent adverse events (TEAEs) by treatment group – safety population.

TEAE n (%)	Tecemotide + Cyclophosphamide (n = 79)	Placebo + Saline (n = 42)
Any grade, n (%)	69 (87.3%)	40 (95.2%)
Grade 3/4, n (%)	23 (29.1%)	11 (26.2%)
Treatment-related, n (%)	38 (48.1%)	20 (47.6%)
Treatment-related Grade 3/4, n (%)	4 (5.1%)	0 (0%)
Fatal TEAE, n (%)	2 (2.5%)	0 (0%)

TEAEs are represented for the number (%) of patients for the two treatment arms respectively (each patient is counted once). Grading according to NCI-CTCAE Version 3.0. **Abbreviations**: NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events, TEAE: treatment-emergent adverse event

48.1% of patients receiving tecemotide and 47.6% of patients receiving placebo, with possibly treatment-related grade 3/4 TEAEs occurring in 5.1% and none of the patients, respectively. In the tecemotide arm, serious TEAE and treatment-related serious TEAE were reported for 27.8% and 5.1% of patients, respectively. In the placebo arm, serious TEAEs were recorded for 31.0% of patients. Most frequent treatment-related (tecemotide+CP) adverse events reported in the tecemotide arm were injection site reaction (25.3%), nausea (16.5%), fatigue (8.9%), and diarrhea (5.1%), in the placebo arm injection site reaction (11.9%), pruritus (9.5%), and diarrhea (7.1%).

Two deaths were reported as TEAEs in the tecemotide arm. One death due to Merkel cell carcinoma was assessed by the investigator as being potentially related to vaccination 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 (one patient from the placebo arm developed prostate cancer, which was assessed as not related to study medication, more than two years after the first vaccination). Another patient treated with tecemotide died of respiratory failure, considered not related to tecemotide by both the investigator and the sponsor.

TEAEs of special interest observed in the tecemotide arm were thrombocytopenia (grade 1) in two patients and alkaline phosphatase increased (grade 3) in one patient. One event of thrombocytopenia was assessed as related to the study drug. In the placebo arm, TEAEs of special interest were thrombocytopenia (grade 1 and grade 2, 1 patient each), alkaline phosphatase increased (grade 2, 1 patient) and AST increased (grade 3, 1 patient), which were all assessed as not related to the study drug.

Discussion

The LICC study failed to demonstrate a benefit of tecemotide compared with placebo for the co-primary endpoints RFS and 3-year OS rate in mCRC patients with LLD after resection of CRLM. Remarkably long survival times were observed in both arms which may partly result from favorable baseline patient and tumor characteristics (median age 60 years, 70% ECOG 0,

Table 3. Incidence and severity of treatment-emergent adverse events (TEAEs) by treatment group and by severity – safety population; Grade1/2 events are listed if ≥10% of patients were affected, grade 3/4 events are listed if at least two patients were affected.

	TEAE grade 1/2 (≥10% patients)	
Preferred term	Tecemotide + Cyclophosphamide n = 79	PLACEBO + Saline n = 42
Nausea	22 (27.8%)	8 (19.0%)
Injection site reaction	21 (26.6%)	6 (14.3%)
Fatigue	18 (22.8%)	8 (19.0%)
Viral upper respiratory tract infection	14 (17.7%)	4 (9.5%)
Diarrhea	12 (15.2%)	5 (11.9%)
Abdominal pain	8 (10.1%)	7 (16.7%)
Hypertension	7 (8.9%)	5 (11.9%)
Rash	6 (7.6%)	5 (11.9%)
Arthralgia	5 (6.3%)	5 (11.9%)
Pruritus	3 (3.8%)	6 (14.3%)
Flatulence	2 (2.5%)	6 (14.3%)
Vomiting	3 (3.8%)	6 (14.3%)
	TEAE grade 3/4 (≥2 patients)	
Diarrhea	2 (2.5%)	2 (4.8%)
Cholestasis	1 (1.3%)	2 (4.8%)
Injection site reaction	2 (2.5%)	-
Back pain	2 (2.5%)	-
Anemia	2 (2.5%)	-
Blood uric acid increased	2 (2.5%)	-
Blood bilirubin increased	1 (1.3%)	1 (2.4%)
Gastritis	1 (1.3%)	1 (2.4%)
Intestinal perforation	1 (1.3%)	1 (2.4%)
Deep vein thrombosis	1 (1.3%)	1 (2.4%)

TEAEs are represented for the number (%) of patients for the two treatment arms respectively. Grading according to NCI-CTCAE Version 3.0., sorted by CTC grades 1/2 and grade 3/4. Patients can be in more than one preferred term category, the highest grade for each patient is counted. Injection site reaction was defined as any event having a preferred term that equals to injection site erythema, injection site reaction, injection site swelling, injection site induration, injection site rash, procedural pain, injection site nodule, injection site pain, injection site pruritus, vaccination site nodule, injection site hematoma or injection site warmth. Abdominal pain was defined as any event having a preferred term that equals to abdominal pain, upper abdominal pain or lower abdominal pain. Intestinal perforation was defined as any event having a preferred term that equals to small intestinal perforation or large intestine perforation. Rash was defined as any event having a preferred term that equals to rash, acne, dermatitis acneiform, rash maculopapular or rash vesicular. Hypertension was defined as any event having a preferred term that equals to hypertension or blood pressure increased. Pruritus was defined as any event having a preferred term that equals to pruritus or pruritus generalized. Deep vein thrombosis was defined as any event having a preferred term that equals to deep vein thrombosis or subclavian vein thrombosis. **Abbreviations**: NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events, TEAE: treatment-emergent adverse event

almost 90% R0 resected, >60% with Fong score 0–2). The work by Fong et al.[25] attributed median survival times of 74, 51, and 47 months to patients with Fong score classifications of 0, 1, and 2 after resection of liver metastasis.

No standard guidelines exist for the surveillance in stage IV mCRC and especially in patients after secondary hepatic resection. Therefore, in clinical routine surveillance is defined by the treating oncologist. In LICC, clinical evaluations were conducted regularly throughout the whole treatment period, with evaluations every 12 weeks during the maintenance treatment period for two years, including physical examination, ECOG performance status, vital signs, and laboratory. CT scans or MRI measurements were carried out alternating with US measurements every six weeks. This close surveillance may have contributed to the beneficial clinical outcome.

The unexpected better, though not significant outcome for the placebo arm may in part be explained by slightly more favorable patient and tumor characteristics (younger age, higher percentage with ECOG 0 and primary resection). However, patients in the tecemotide arm presented with less metastases and a lower portion with a high-risk Fong score. Moreover, rectal carcinomas were less frequent in the placebo arm.

A potential influence of placebo composition on the study outcome is rated as unlikely. The placebo contained the same carrier lipid matrix as the vaccine but lacked MPLA and MUC1 lipopeptide BLP25. The absence of *RAS* and *BRAF* mutation status information may not allow us to see a molecular bias between treatment arms.

Alkylating agents in general, especially cyclophosphamide, can elicit an antitumor immune response in the context of active or adoptive immunotherapy by directly affecting the activity of T lymphocytes and natural killer cells as well as by reducing the number of regulatory T cells (Treg) and their functionality. Cyclophosphamide-induced Treg depletion may trigger a clinically relevant boost in antitumor immunity.[26–29] Thus, low-dose cyclophosphamide as administered in the tecemotide arm may have had an effect on the survival outcomes reported in the LICC trial.

Resection status had the most pronounced impact on RFS in Cox proportional hazards regression analysis. This is in accordance with various publications that have listed resection status among the most relevant prognostic factors for mCRC patients with resected CRLM,[30–33] and assigned an influence on long-term survival.[25] While MUC1 expression status has been described as an indicator of poor prognosis for mCRC patients[34–36] and as a predictor of RFS and OS,[37] the assessment of its role remains controversial.[38–40] The LICC study did not confirm an association between MUC1 expression status and efficacy outcomes.

Many TEAEs assessed as related to study medication concerned injection site reactions and flu-like symptoms, which is

consistent with reported safety analyses for the tecemotide formulation.[20,41,42]

Survival times in LICC equal those of primarily resected patients treated with peri- or postoperative chemotherapy[10,11] and are longer than those for secondarily resected patients in the previously published EORTC and FFCD trials.[12,13] This may partly be explained by the inclusion of both primarily (66%) and secondarily (34%) resected patients. Naturally, such comparisons are hampered by differences in baseline characteristics (LICC: median age of 60 years; <5 resected metastases 86%, 5–10 resected metastases: 11.6%; EORTC: median age 63 years, up to 4 metastases; FFCD: 1–3 metastases 95.3%).

It is important to consider the limitations of the LICC trial, which was designed as a signal finding study. Thus, all statistical analyses have to be considered as explorative. The relatively high fraction of censored patients and the low number of patients in subgroup analyses limit the value of the Kaplan-Meier survival curves. At study closure, a considerable fraction of patients (45%) was alive. Thus, OS and RFS data must be interpreted with caution. More mature data may be gained in a future long-term analysis. Results from a translational research program on immuno-monitoring parameters that accompanied the LICC trial will be published separately and may provide further insight.

The repeated failure of immunotherapeutic approaches in colorectal cancer, either of vaccination strategies[43] or checkpoint inhibitors[44] is not well understood. More translational data are urgently needed to enable us to better serve our patients. Trials combining vaccination therapy and checkpoint inhibitors may be an option for future trials.

Conclusion

The LICC trial failed to meet its primary endpoint of significantly improving RFS and 3-year OS rate with tecemotide. MUC1 expression was not associated with the outcome. Nevertheless, patients in both arms showed a better OS compared to historical controls. Next to favorable patient and tumor characteristics, more selective surgery and improved resection techniques due to later study conduct as well as a close surveillance program, which lead to early re-treatment in the case of detected recurrence, may have positively influenced patient survival.

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Disclosure of interest

Disclaimers

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