Received: 27 May 2021 | Revised: 27 September 2021 | Accepted: 14 October 2021

DOI: 10.1002/ijc.33881

CANCER THERAPY AND PREVENTION

IJC INTERNATIONAL JOURNAL of CANCER

Survival after secondary liver resection in metastatic colorectal cancer: Comparing data of three prospective randomized European trials (LICC, CELIM, FIRE-3)

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Abbreviations: CHT, chemotherapy; CI, confidence interval; CT, computed tomography scan; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten Rat sarcoma viral oncogene; LLD, liver-limited disease; mCRC, metastatic colorectal cancer; OS, overall survival; RFS, recurrence-free survival.

All funders had no role in study design, data collection and analysis, interpretation of results, decision to publish or preparation of the manuscript.

The authors confirm that this work has not been published previously. Parts of this comparison as well as the final results of the LICC study itself have been presented at the ASCO-GI 2019. The latter has also been presented at the ASCO Annual Meeting 2019 and the original article was published in 2020 (doi: 10.1080/2162402X.2020.1806680). Another original article on LICC was published in 2012 (doi: 10.1186/1471-2407-12-144). Original articles were also published on CELIM (doi: 10.1016/S1470-2045[09]70330-4; doi: 10.1093/annonc/mdu088) and on FIRE-3 (doi: 10.1016/S1470-2045[14]70330-4; doi: 10.1002/ijc.31114).

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Funding information
The LICC study was designed, managed and analyzed by the University of Mainz Medical Center, Department of Gastroenterology and iOMEDICO and received financial support from Merck KGaA, Darmstadt, Germany. The LICC trial was supported by a medical grant and supply of drugs from Merck KGaA, Darmstadt, Germany.

Abstract

Metastatic colorectal cancer (mCRC) patients with liver-limited disease (LLD) have a chance of long-term survival and potential cure after hepatic metastasectomy. However, the appropriate postoperative treatment strategy is still controversial. The CELIM and FIRE-3 studies demonstrated that secondary hepatic resection significantly improved overall survival (OS). The objective of this analysis was to compare these favorable outcome data with recent results from the LICC trial investigating the antigen-specific cancer vaccine tecemotide (L-BLP25) as adjuvant therapy in mCRC patients with LLD after R0/R1 resection. Data from mCRC patients with LLD and secondary hepatic resection from each study were analyzed for efficacy outcomes based on patient characteristics, treatment and surveillance after surgery. In LICC, 40/121 (33%) patients, in CELIM 36/111 (32%) and in FIRE-3-LLD 29/133 (22%) patients were secondarily resected, respectively. Of those, 31 (77.5%) patients in LICC and all patients in CELIM were R0 resected. Median disease-free survival after resection was 8.9 months in LICC, 9.9 months in CELIM. Median OS in secondarily resected patients was 66.1 months in LICC, 53.9 months in CELIM and 56.2 months in FIRE-3-LLD. Median age was about 5 years less in LICC compared to CELIM and FIRE-3. Secondarily resected patients of LICC, CELIM and FIRE-3 showed an impressive median survival with a tendency for improved survival for patients in the LICC trial. A younger patient cohort but also more selective surgery, improved resection techniques, deep responses and a close surveillance program after surgery in the LICC trial may have had a positive impact on survival.

KEYWORDS
CELIM, colorectal cancer, FIRE-3, LICC, liver-limited disease, secondary resection

What's new?

The management of liver-limited disease (LLD) in patients with metastatic colorectal cancer (mCRC) is controversial, the optimal treatment has not been defined. Here, data from mCRC patients with LLD and secondary hepatic resection from the prospective randomized trials CELIM, FIRE-3 and LICC were compared. Secondarily resected patients from these trials showed an impressive overall survival (OS), with a tendency for improved OS in LICC. Reasons might be the deep response induced by chemotherapy and surgery combined with close surveillance after surgery. Further prospective, randomized clinical trials are strongly needed to clarify these benefits.

1 | INTRODUCTION

Complete hepatic metastasectomy provides a chance of long-term survival and potential cure to metastatic colorectal cancer (mCRC) patients with liver-limited disease (LLD).[1-3] In the last decades, long-term survival for mCRC patients has improved markedly, with 5-year overall survival (OS) rates nearly doubling, from around 30% to approximately 50% since the 1980s.[1,4-7]

Resection of metastases is recommended for patients with Stage IV colorectal cancer (CRC) with LLD if surgery is feasible.[8] Yet, more than 80% of patients are not eligible for surgery.[4,9] For these patients, downstaging may be achieved by the administration

of systemic chemotherapy (CHT).[8] Due to the damaging effect, that CHT may have on healthy liver tissue, the NCCN guidelines recommend resection once it becomes feasible after systemic therapy.[10] In case unresectable metastasis persists, a regular re-evaluation of resectability should be performed every 8 weeks.[8,10] Approximately 22% to 40% of patients become resectable after systemic therapy.[11-14] The prognostic value of liver resection has been reported before: the comparison of patients with R0 resection vs

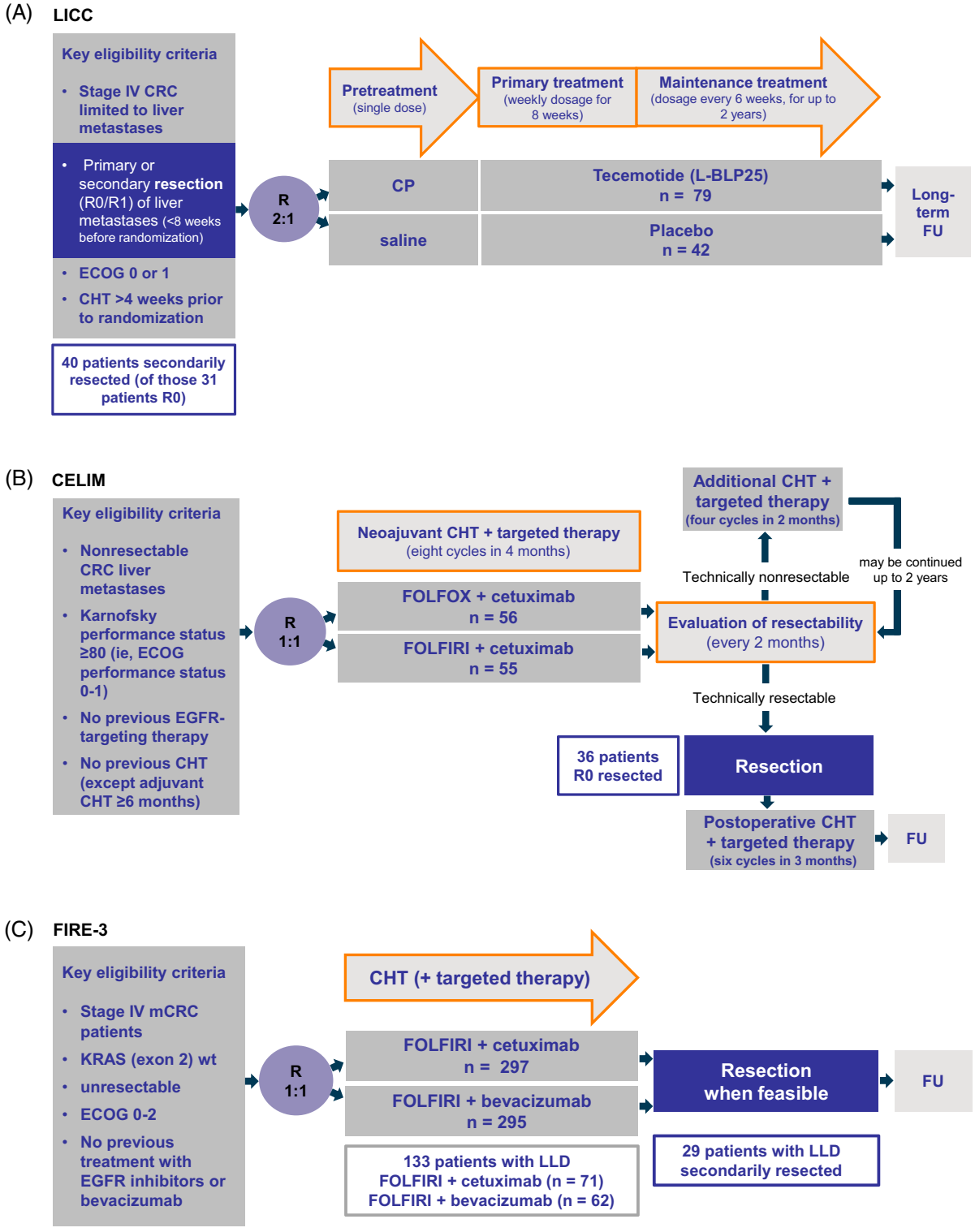

FIGURE 1 Study designs of (A) the LICC trial, (B) the CELIM trial and (C) the FIRE-3 trial including subgroup analysis of Holch et al,[12] involving patients with LLD and KRAS exon 2 wild-type only. CHT, chemotherapy; CP, cyclophosphamide; (m)CRC, (metastatic) colorectal cancer; ECOG, Eastern Cooperative Oncology Group; FU, follow-up; KRAS, Kirsten Rat sarcoma viral oncogene; LLD, liver-limited disease; R, randomization; wt, wild type [Color figure can be viewed at wileyonlinelibrary.com]

patients without resection revealed a hazard ratio of 0.42 (95% confidence interval [CI], 0.21-0.86; $P = .021$) regarding OS in the CELIM trial.[13] Long-term survival of mCRC patients after secondary resection of liver metastases, that is, resection after initial systemic treatment, is comparable to that of primarily resected patients.[15,16] Median survival times of 55 months[12,13] and a 5-year survival rate of 46%[13] vs 46.4 to 62.1 months and 42% to 48%[4,6] were reported for patients after secondary and primary resection, respectively.

Data on clinical and molecular markers that might contribute to prolongation of survival are rare and optimal follow-up following resection is still under debate. High recurrence rates of more than 50% after R0 resection of liver metastases[14,17,18] remain a challenge. Furthermore, the choice of the appropriate postoperative treatment strategy is still controversial. The German S3-Guideline does not recommend adjuvant CHT after R0 resection of hepatic metastases due to lack of evidence for a clear benefit.[8] In comparison, the European Society for Medical Oncology (ESMO) consensus guidelines indicate a potential benefit from adjuvant therapy for patients with unfavorable oncological and surgical criteria.[19] Guidelines furthermore recommend a structured postresection surveillance and follow-up for patients with colorectal carcinoma Stage IV following curative metastasectomy.[8] The LICC trial recently evaluated tecemotide (L-BLP25) as antigen-specific cancer vaccine targeting mucin 1 (MUC1) as an adjuvant therapy in mCRC patients after R0/R1 LLD resection.[20,21]

This work compares the efficacy results for secondarily resected LLD patients of the LICC trial with two trials as historical controls: the CELIM trial[13,22] and an analysis of the LLD subgroup of the FIRE-3 study.[12,23] Differences in baseline characteristics, treatments and surveillance after metastasectomy are taken under consideration.

The CELIM trial evaluated the effect of neoadjuvant treatment in primarily unresectable LLD mCRC patients. The FIRE-3 trial compared FOLFIRI plus cetuximab vs FOLFIRI plus bevacizumab as first-line treatment in patients with unresectable mCRC. The retrospective subgroup analysis of the FIRE-3 study (FIRE-3-LLD subgroup)[12] included patients with initially unresectable Kirsten Rat sarcoma viral oncogene (KRAS) exon 2 wild-type mCRC with LLD.

TABLE 1 Patient characteristics at baseline

	LICC (all pts)[a]	CELIM (all pts)[a]	FIRE-3 (LLD pts only)[a]
Patient population (n)	121	111	133
Median age (y)	60.0	Arm A: 65.1 Arm B: 62.0	66
Primary tumor stage, n (%)	*T1/2* 16 (13.2) *T3/4* 101 (83.5)	*T1/2* 15 (13.5) *T3/4* 92 (82.9)	*T1/2* 19 (14.3) *T3/4* 106 (79.9)
Primary tumor site, n (%)	*Colon* 73 (60.3) *Rectum* 48 (39.7)	*Colon* 61 (55.0) *Rectum* 49 (44.1)	*Colon* 90 (67.7) *Rectum* 41 (30.8)
Median time since first diagnosis (mo) (min-max)	18.3 (0.9-121.3)	NA	NA
Any comorbidity	102 (84.3)	NA	NA
ECOG performance status, n (%)	ECOG 0: 85 (70.2) ECOG 1: 36 (29.8)	KPS ≥ 80% (ECOG 0/1)	ECOG 0: 69 (51.9) ECOG 1: 64 (48.1)
Metastases, n (%)	*Resected metastases* <5: 104 (86.0) 5-10: 14 (11.6) >10: 3 (2.5)	*Number of metastases* <5: 30 (27.0) 5-10: 58 (52.3) >10: 19 (17.1)	NA
Prior neoadjuvant chemotherapy, n (%)	83 (68.6)[b]	18 (16.2)[c]	10 (7.5)[c]
Patient population of analyzed subgroup, n (%)	40 (33.1)	36 (32.4)	29 (21.8)
Resection status, n (%)[d]	R0: 31 (77.5) R1: 9 (22.5)	R0: 36 (100.0)	NA

Abbreviations: ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; LLD, liver-limited disease; NA, not applicable/not available; pts, patients.

[a]Numbers given are pooled across the treatment arms.

[b]Greater than or equal to 4 weeks before randomization.

[c]Greater than or equal to 6 months before trial start.

[d]Of patients within the analyzed subgroup of secondary resected patients.

2 | PATIENTS AND METHODS

2.1 | Studies

The LICC trial was a binational, multicenter, randomized, double-blinded Phase II study.[20] The CELIM Phase II trial and the FIRE-3 Phase III trial were both multicenter, randomized, open-label studies.[22,23] All three trials included patients with Stage IV mCRC who had metastases limited to the liver and had undergone secondary hepatic resection with curative intent (R0 or R1). Curative resection of liver metastases was an eligibility criterion for patients to be included in LICC whereas it was an endpoint in the CELIM and FIRE-3 studies. The study designs of the three studies are shown in Figure 1. In total, 40 patients of the LICC trial, 36 patients of the CELIM trial and 29 patients from FIRE-3 underwent secondary resection and are analyzed in this analysis.

2.2 | Treatment

LICC patients received adjuvant tecemotide or placebo after secondary LLD resection as eight weekly doses, followed by 6-week maintenance intervals and tight surveillance until recurrence or a maximum of 2 years. In the CELIM trial, patients with primarily unresectable disease received neoadjuvant CHT, either with FOLFOX6 and cetuximab (Arm A) or FOLFIRI and cetuximab (Arm B) until resectability of liver metastases was feasible or disease progression. Resection was followed by postoperative CHT and long-term follow-up for a maximum of 5 years. Patients in the FIRE-3 trial received either FOLFIRI and cetuximab (Arm A) or FOLFIRI and bevacizumab (Arm B) as first-line treatment. Treatment was continued until disease progression, complete response or until surgical resection became possible. Patients were followed up for a maximum of 5 years.

2.3 | Statistical considerations regarding comparability of efficacy outcomes

Recurrence-free survival (RFS) in the LICC trial was calculated from the date of randomization, that is, within 8 weeks after resection. Disease-free survival (DFS) in the CELIM trial was calculated from the date of resection. In LICC, CELIM and FIRE-3, OS was calculated from the date of randomization, which was after secondary resection in the LICC study and before "neoadjuvant" therapy for CELIM and FIRE-3. Progression-free survival in CELIM was calculated from the date of randomization.

3 | RESULTS

3.1 | Patient characteristics at baseline

In the LICC trial, patients were enrolled between October 2011 and December 2014. In total, 121 patients were randomized 2:1 to receive either adjuvant tecemotide or placebo. Of these, 40 patients (33.9%) had been secondarily resected. R0 resection was achieved in 31 patients (77.5%).

Patients were enrolled into the CELIM trial from December 2004 until March 2008. A total of 111 patients were randomized 1:1 into Arm A (FOLFOX6 and cetuximab) or Arm B (FOLFIRI and cetuximab); 36 of those patients with primarily unresectable LLD could be secondarily R0 resected (32.4%) during the study.

The FIRE-3 study enrolled patients between January 2007 and September 2012. In total, 752 patients were randomized 1:1 to Arm A (FOLFIRI plus cetuximab) or Arm B (FOLFIRI plus bevacizumab). The subgroup analysis (RAS-WT population of FIRE-3) by Holch et al involved 400 patients from which 133 patients presented with LLD.[12] Secondary resection was performed in 29 of those patients (21.8%).

Patient characteristics at baseline are shown in Table 1. The LICC trial showed more favorable prognostic parameters for age (median age about 5 years less), more patients with Eastern Cooperative Oncology Group (ECOG) 0 status (70.2%) and a relatively high proportion of patients with ≤5 metastases (86.0%). Notably, in CELIM, one key eligibility criterion was nonresectability of liver metastases (ie, ≥5 metastases or technically nonresectable).

TABLE 2 Efficacy outcomes of the subgroup analysis of the LICC trial, CELIM trial and FIRE-3-LLD of patients with LLD and secondary resection

Outcome	Secondary resection status	LICC	CELIM	FIRE-3 LLD
mRFS (mo) (95% CI)	R0 + R1	6.1 (3.7-11.3)		NA
	R0	8.9 (5.0-16.8)	9.9 (5.8-14.0)	
	R1	3.2 (1.9-6.6)		
mOS (mo) (95% CI)	R0 + R1	66.1 (38.3-NA)		56.2
	R0	73.9 (43.0-NA)	53.9 (35.9-71.9)	
	R1	38.3 (17.8-NA)		

Abbreviations: CI, confidence interval; LLD, liver-limited disease; mOS, median overall survival; mRFS, median recurrence-free survival; NA, not applicable/not available.

3.2 | Efficacy outcomes

For all three trials, efficacy results are shown for the total population of secondarily resected patients (Table 2). In the LICC trial, for secondarily resected patients, DFS was 8.9 months (95% CI, 5.0-16.8) after R0 resection and 3.2 months (95% CI, 1.9-6.6) for R1 resected patients. In CELIM, patients had a median DFS of 9.9 months (95% CI, 5.8-14.0) after R0 resection.

Median OS in the LICC trial for secondarily resected patients was 66.1 months (95% CI, 38.3-NA) with 38.3 months (95% CI, 17.8-NA) for the R1 subgroup and 73.9 months (95% CI, 43.0-NA) for the R0 subgroup at time of analysis. In CELIM, median OS was 53.9 months (95% CI, 35.9-71.9) for R0 resected patients. In the FIRE-3-LLD subgroup, median OS was 56.2 months after secondary resection (Table 2).

RFS and OS data for secondarily resected patients for the subgroups of R0 and R1 resected patients of the LICC and the CELIM trials are shown as Kaplan-Meier survival analyses in Figures 2 and 3.

3.3 | Surveillance program

In LICC, clinical evaluations were conducted regularly throughout the whole treatment period after resection, with evaluations every 12 weeks during the maintenance treatment period for 2 years, including physical examination, ECOG performance status, vital signs and laboratory. Computed tomography scan (CT) or magnetic resonance imaging measurements and ultrasound measurements were carried out alternating every 6 weeks.

In CELIM, follow-up assessments following resection were carried out according to clinical routine. In the FIRE-3 study, tumor response assessments were performed every 3 months after resection. Surveillance programs of the three studies are compared in Figure 4.

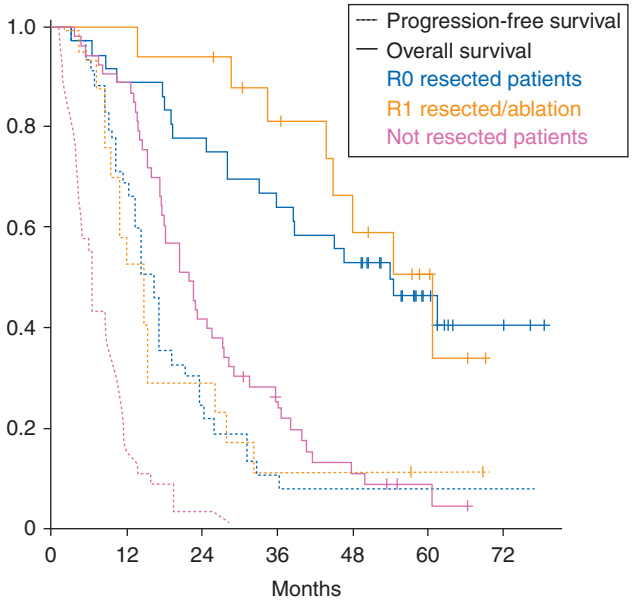

FIGURE 3 CELIM trial Kaplan-Meier curves for progression-free survival and overall survival depending on resection; R0 resection (blue), R1 resection or radiofrequency ablation with or without R0/R1 resection (orange), no resection (pink). Figure published in Folprecht et al[13] [Color figure can be viewed at wileyonlinelibrary.com]

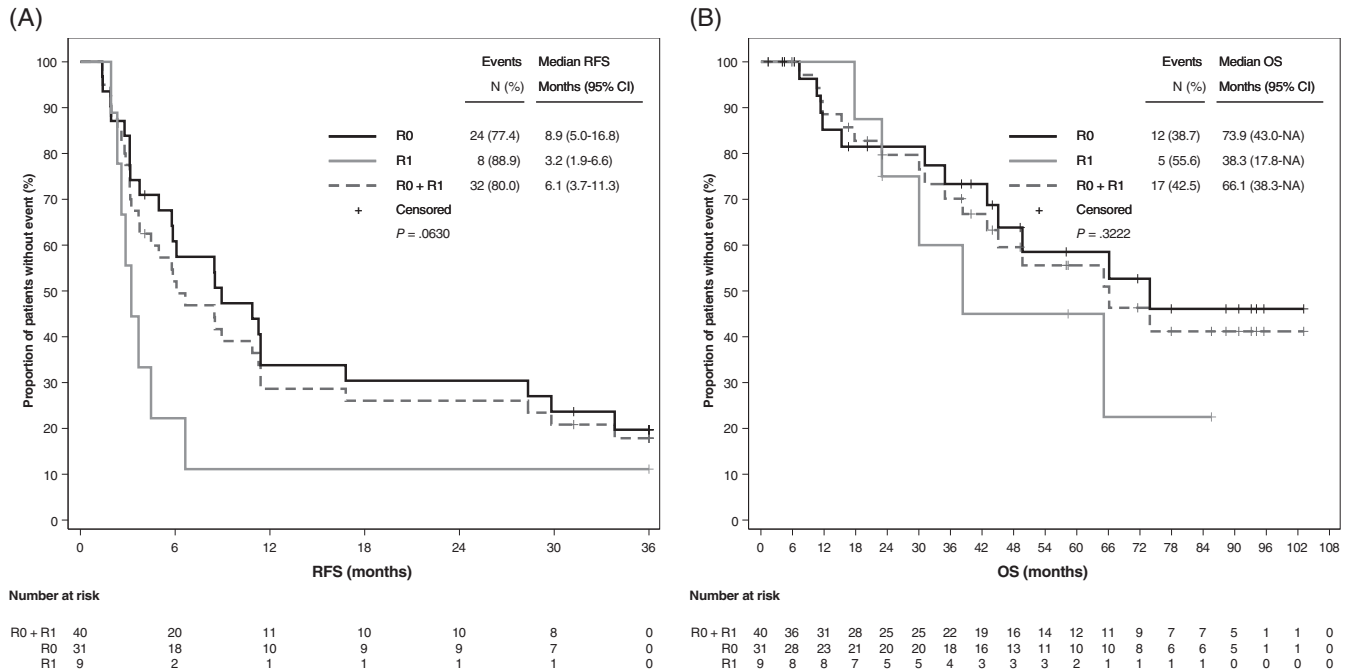

FIGURE 2 LICC trial Kaplan-Meier curves for secondarily resected patients with R0 and R1 resection status, (A) recurrence-free survival and (B) overall survival

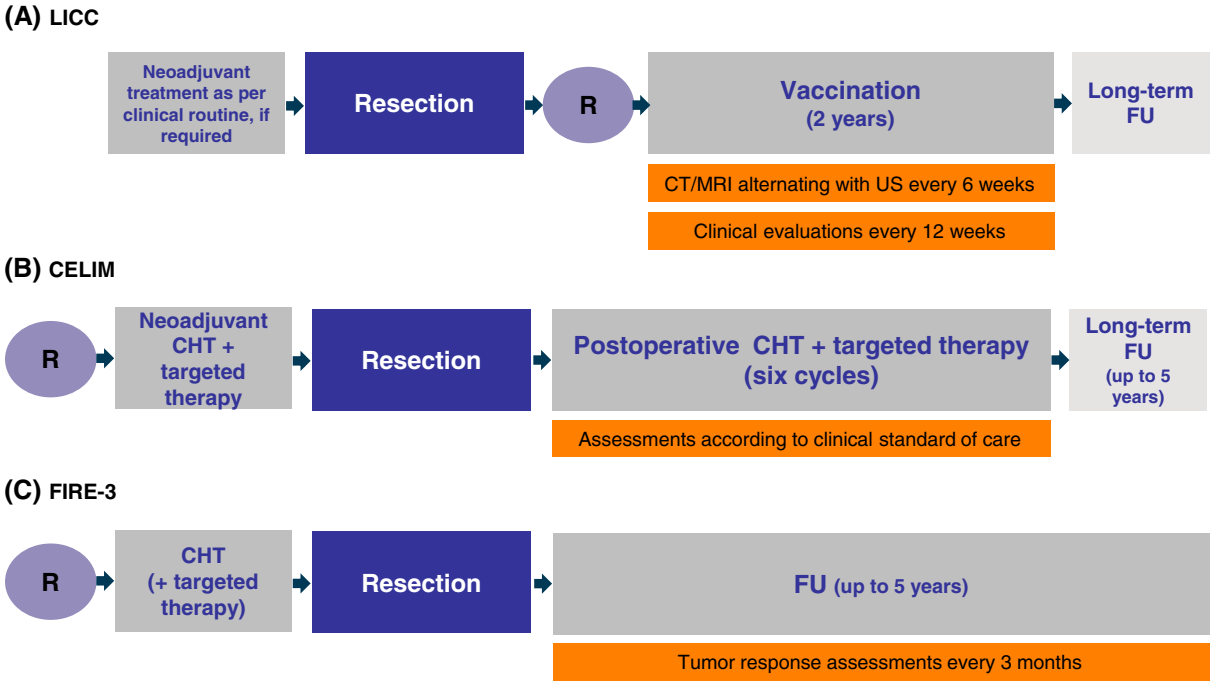

FIGURE 4 Comparison of surveillance in the LICC trial, the CELIM trial and the FIRE-3 trial. CHT, chemotherapy; CT, computed tomography scan; FU, follow-up; MRI, magnetic resonance imaging; R, randomization; US, ultrasound [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

The objective of the comparison of data from secondarily resected patients of the LICC, CELIM and FIRE-3 studies was to identify factors that potentially have an impact on survival outcome.

In recent decades, efforts were made to prolong survival after surgery using different adjuvant therapies and treatment regimens,[21,24] but most attempts did not lead to an improved survival.

In CELIM, patients received either FOLFOX plus cetuximab or FOLFIRI plus cetuximab as perioperative treatment, whereas six cycles were given as postoperative, adjuvant treatment. In FIRE-3, either FOLFIRI plus cetuximab or FOLFIRI plus bevacizumab were administered prior to secondary resection and no adjuvant treatment was prescribed. In LICC, patients received adjuvant treatment with tecemotide or placebo after resection. The secondarily resected patients that were compared in this analysis represent about one-third of all study patients for LICC and CELIM (33.9% and 32.4%, respectively) and 21.8% of FIRE-3 patients with LLD. Patients in LICC were about 5 years younger than LLD patients in CELIM and FIRE-3 and the number of resected metastases was on average lower compared to CELIM.

Median RFS times were comparable between LICC and CELIM. Median OS times were impressive for all three studies with even longer survival times for patients within the LICC trial. Especially, considering that OS times in LICC are underestimated as they were calculated from date of randomization which was after resection whereas OS times in CELIM and FIRE-3 were calculated from start of neoadjuvant treatment. Different factors could contribute to this difference. Patients in LICC were younger than patients in the other studies and presented with a lower number of metastases, which has been associated with better survival.[4] As LICC was the most recent of the three studies, increased survival results might also be explained by multiple improvements in the treatment of CRC during the last decades, comprising surgical resection techniques and systemic therapies, an increase in multidisciplinary teams, as well as improvements in imaging and prognostic and predictive markers.[19] In literature, improved outcomes in mCRC have been attributed to increased resection rates and improved therapies,[25] as well as to improved preoperative imaging and improved surgery.[4]

The role of postresection surveillance as a factor for prolonged survival times is not yet clear. Currently, although S3-guidelines recommend a structured surveillance and follow-up for patients with colorectal cancer Stage IV after curative metastasectomy[8] and NCCN guidelines suggests a similar surveillance as for patients with Stage II/III CRC but with certain evaluations being performed more frequently,[10] no clear standard guidelines currently exist for surveillance in Stage IV mCRC and especially in patients after secondary hepatic resection. Thus, in clinical routine, surveillance is mainly defined by the treating oncologist. In a recent publication by Monteil et al, a surveillance program was performed in CRC patients Stage II/III after surgery, comparing six monthly positron emission tomography (PET)/CT combined with clinical exams every 3 months to conventional follow-up (clinical exams every 3 month, liver sonography every 6 months and lung radiography or CT every 12 months) over 3 years.[26] In this study, the PET/CT-arm could not increase the rate of detected recurrence at 3 years and did not increase survival. Surveillance after resection in the LICC study was even more close, with detailed evaluations every 12 weeks and evaluations using

imaging techniques every 6 weeks, and could be an important factor contribution to prolonged survival times compared to CELIM and FIRE-3, where surveillance equaled conventional follow up routine. At this point, the possibility of lead time bias has to be considered. Close surveillance allows to identify a relapse earlier, and thus further treatment could be initiated earlier which might result in longer survival.

More prospective studies are needed to investigate the optimal approach of surveillance after resection of Stage IV patients to provide clinicians with guidelines on how tight surveillance programs should be to ensure best possible survival options.

Our comparison of the three studies has limitations. It has to be considered that study designs were different and study therapy applied to different treatment timepoints in the three studies. In all three trials, information concerning baseline characteristics were not available for the subpopulations of secondarily resected patients. Furthermore, in all three studies, the analyzed subgroup of secondarily resected patients was relatively small and it has to be considered, that the CELIM trial and FIRE-3-LLD subgroup analysis involved only patients with KRAS exon 2 wild type, while in LICC, RAS mutation status was not defined and patients with RAS mutant tumor and worse prognosis were included, too. Also, preoperative staging and evaluations of resectability were different. Whereas in LICC, resectability was judged and resection was performed according to local standard, for example, the local multidisciplinary tumor board, prior to randomization; in CELIM, resectability was assessed post hoc by a team of surgical experts who also recruited patients for the trial. In FIRE-3, resectability was assessed locally, with the recommendation in the study protocol of involving a multidisciplinary team. Since the decision to resect colorectal liver metastases is driven by several issues such as technical considerations, prognostic factors for early recurrence as well as attitudes of the treating physicians, a certain subjective component in the decision-making process cannot be excluded.[22]

5 | CONCLUSION

Secondarily resected patients of LICC, CELIM and FIRE-3 showed impressive median OS with a tendency of improved OS for patients within the LICC trial which had enrolled a younger patient cohort. The LICC trial provided a median OS of 66.1 months which, to our knowledge, is the best outcome reported for secondarily R0/R1 resected mCRC patients with LLD. Apart from the limitations discussed, other factors such as more selective surgery, improved resection techniques, the deep response due to complete remission induced by secondary surgery and the close surveillance program after surgery in the LICC trial may have positively impacted survival. Further large prospective randomized clinical trials are strongly needed to completely answer the research question.

ACKNOWLEDGMENTS

The authors thank all patients, physicians and study teams participating in LICC, CELIM and FIRE-3. The authors thank Dr Bettina Kinkel (iOMEDICO) and Dr Judith Czarnecki (iOMEDICO) for preparation of the manuscript. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

Markus Moehler: Honoraria or consulting or advisory role: Falk, Nordic Amgen, AstraZeneca, mcI, Frankfurt, Lilly, MSD, MerckSerono, BMS, Pfizer, Roche; Research funding: Amgen, BMS, MSD, Merck Serono, EORTC; Travel, accommodations, expenses: Merck Serono, BMS, Roche, MSD, Amgen. **Gunnar Folprecht**: Honoraria: Merck, Roche/Genentech, BMS, Sanofi-Aventis, Servier, Lilly, MSD; Consulting or advisory role: Merck, Roche/Genentech, BMS, Bayer, MSD, Sanofi-Aventis, Servier; Research funding: Merck-Serono. **Volker Heinemann**: Honoraria: Merck, Amgen, Sanofi, SIRTEX, Servier, Roche; Consulting or advisory role: Merck, Amgen, Sanofi, SIRTEX, Servier, Roche; Speaker's bureau: Merck, Amgen, SIRTEX, Servier, Roche; Research funding: Merck, Pfizer, Roche, Amgen, SIRTEX, Servier; Expert testimony: Servier; Travel, accommodations, expenses: Merck, Roche, Amgen, Servier, SIRTEX; other relationships to disclose: Merck, Roche, Amgen, SIRTEX, Servier. **Julian Walter Holch**: Honoraria: Roche; Consulting or advisory role: Roche; Speaker's bureau: Roche; travel, accommodations, expenses: Roche, Novartis. **Annett Maderer**: Patents, Royalties, other intellectual property: J.-G. University Mainz. **Stefan Kasper**: Honoraria: BMS, Amgen, Servier, Merck, Roche, MSD; Consulting or advisory role: BMS, Amgen, Servier, Roche, Merck, MSD; Research funding: BMS, Celgene, Merck, Lilly; Travel, accommodations, expenses: Roche, Merck, Amgen, Lilly, BMS. **Friedrich Overkamp**: Honoraria: Amgen, AstraZeneca, Bayer, BMS, Boehringer, Chugai, Celgene, Gilead, Ipsen, Janssen, Merck, MSD, Novartis, Riemser; Consulting or advisory role: Amgen, BMS, Boehringer, Cellox, ClinSol, Hexal, Iomedico, MSD, Novartis, Riemser, Roche, Tesaro, Teva. **Wolf Otto Bechstein**: Honoraria: Astellas, Baxter, Integra, MCI-Deutschland, Med-Update, Merck Serono, Teva; Consulting or advisory role: Astellas; Speaker's bureau: Integra. **Matthias Vöhringer**: Consulting or advisory role: Roche (Advisory Board). **Florian Lordick**: Honoraria: Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Elsevier, BioNTech AG, SERVIER, Infomedica, Merck KGaA, Roche; Consulting or advisory role: Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, Astellas Pharma; Research funding: Bristol-Myers Squibb; Travel, accommodations, expenses: Bristol-Myers Squibb. **Irene Schmidtmann**: Research funding: Merck-Serono. **Carl Christoph Schimanski**: Employment: Merck (immediate family member); Research funding: Merck supported LICC trial, sponsor University of Mainz received all payments; Travel, accommodations, expenses: Gilead 2018, German GI meeting. All the other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this work are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Like the CELIM trial and the FIRE-3 trial, the LICC trial was conducted according to the ethical principles of the declaration of Helsinki. The

study protocol was reviewed by the independent ethics committee or the institutional review board for each center. Each patient had provided written informed consent before screening procedures were initiated. All three studies were registered at ClinicalTrials.gov (LICC: NCT01462513, FIRE-3: NCT00433927, CELIM: NCT00153998).

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How to cite this article: Moehler M, Folprecht G, Heinemann V, et al. Survival after secondary liver resection in metastatic colorectal cancer: Comparing data of three prospective randomized European trials (LICC, CELIM, FIRE-3). *Int. J. Cancer*. 2022;150(8):1341-1349. doi:10.1002/ijc.33881