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Progress Report

A multicentre, international, observational study on transarterial chemoembolisation in colorectal cancer liver metastases: Design and rationale of CIREL ☆

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ABSTRACT

Background: About 70–80% of patients with colorectal liver metastases appear as ineligible for a curative treatment approach. Transarterial chemoembolisation (TACE) using irinotecan-eluting beads has emerged as a promising treatment option in cases with irresectable liver metastases. Despite being in clinical practice for years, little is known about the treatment characteristics and outcomes when used as per routine hospital practice.

Methods: Patients with hepatic metastases from colorectal cancer origin, admitted to contributing centres to receive TACE with drug-eluting LifePearl® Microspheres loaded with irinotecan, as part of their standard care, will be consecutively added to the registry. Data will be collected until the end of study, loss to follow-up or death. Primary endpoint is the characterisation of the treatment usage at the selected sites in Europe. Secondary endpoints include outcome parameters, safety and toxicity, as well as quality of life.

Conclusion and AIMS: This multicentre, international, prospective observational study conducted in European centres plans to collect real-life data. This data will form an evidence-base from which conclusions can be drawn on how to improve patient selection and optimise treatment protocols when treating with TACE using irinotecan-eluting microspheres.

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1. Introduction

Liver metastases occur in 60–70% of colorectal cancer (CRC) patients and constitute a major cause of death in this population [1]. 20–50% of CRC patients will have hepatic involvement at the time of primary diagnosis [2]. Surgical resection and thermal ablation in selected patients are the only curative option in metastatic patients. However, only about 20% of CRC patients that present with liver metastases are eligible for surgical resection [2].

Interventional radiological procedures, such as tumour ablation, transarterial chemoembolisation (TACE) or radioembolisation (TARE), are options in attempting to control the disease in the liver [2,3] in patients not eligible for curative treatments. During the minimally invasive procedure of TACE, small beads are injected into tumour-supplying arteries and block the blood supply while delivering chemotherapeutic agents to the tumour site. Liver metastases from colorectal cancer are generally treated with beads loaded with active compounds, e.g. a topoisomerase inhibitor like irinotecan [3,4].

In clinical trials and case-control studies hepatic arterial infusion using irinotecan-eluting beads have been demonstrated to be effective and safe [5–8]. Patients with colorectal liver metastases (CRLM) with both resectable and unresectable metastases have been treated with irinotecan-eluting beads in the neoadjuvant setting, aiming for cure in a combined modal approach [9–11], or palliative setting, aiming for a prolonged survival time and a maintenance of good health-related quality of life [9,12], as first-line treatment [7,13–15] and when failing to respond to one [6] or several lines [5,8,16] of systemic treatment with chemotherapeutic drugs.

Despite irinotecan-eluting beads now being available for more than 10 years, until recently most reports are of retrospective nature [17,18]. Prospective real-world data from large cohorts is still lacking.

The *CIrse REgistry for LifePearl® microspheres (CIREL)* will therefore prospectively capture data of patients with CRLM that are being treated with TACE using LifePearl® Microspheres (Terumo Europe N.V., Leuven, Belgium) loaded with irinotecan (LP-IRI). LifePearl® Microspheres are a medical device, certified to treat CRLM by blocking the tumour-supplying arteries, and delivering local chemotherapy, in this case by loading the particles with irinotecan.

The aim of CIREL is to improve our understanding of how LP-IRI is administered as part of the standard treatment of colorectal adenocarcinoma with liver-only or liver-dominant metastases in Europe. The collection of real-life data is intended to form a source of evidence from which conclusions can be drawn on how to improve patient selection and optimise treatment protocols in order to improve the therapeutic outcome of patients treated with TACE with LP-IRI. While we expect the majority of LP-IRI cases to be performed in a relatively late-line therapy setting – which is in line with current European CRC treatment guidelines - we are particularly interested in observing LP-IRI as a combination treatment with systemic chemotherapy or ablation, as well as using LP-IRI treatment to allow intervals without further systemic treatment. A particularly interesting subgroup will be irinotecan-naïve patients.

This observational study is sponsored by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) and funded by an unrestricted educational grant by Terumo Europe NV. Beyond publishing standards of practice guidelines for interventional radiologists, CIRSE has recognised the need to also actively create data in a post-market, observational setting. This is especially relevant considering recent changes in legislation due to EU Regulation 2017/745 on Medical Devices (MDR), which highlights the need for post-market surveillance.

1.1. Patients and study design

CIREL is a prospective, multicentre, single-arm, non-interventional, observational study.

1.2. Eligible patients

All patients with CRLM decided to be treated with LP-IRI by the centre's multidisciplinary tumour board and therefore treated with LP-IRI are eligible.

Eligible centres were selected by CIRSE and meet the selection criteria below:

- Having performed a total of 40 treatments of any liver metastases with drug-eluting beads to date or a total of at least 10 treatments of any liver metastases with drug-eluting beads in the last 12 months
- Having performed at least 1 treatment with LP-IRI
- Are willing to comply with the observational study requirements, including presenting the possibility to participate in the observational study to all subjects that are eligible

This study (clinicaltrials.gov NCT03086096) is performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by local Ethics Committees of participating centres. All patients will provide written informed consent before starting the study.

1.3. Endpoints and assessments

The primary endpoint is to categorise observed usages of LP-IRI as one of the treatment settings and indications displayed in Table 1. Secondary objectives of CIREL will be to assess treatment outcomes in terms of safety, effectiveness and quality of life parameters (see Table 2), including progression-free survival, hepatic progression-free survival, objective response rate, early tumour shrinkage at $\geq$20% and $\geq$30% at first tumour assessment and depth of response. Response parameters will be assessed by the investigator as well as by an independent central image review, performed by the Fédération Francophone de Cancérologie Digestive (FFCD).

1.4. Data collection

Patient data collection will incorporate information obtained before the first LP-IRI treatment, also (retrospectively) capturing disease parameters and previous treatments. Following completion of the treatment session(s) and associated data requirements, follow-up visits are to be conducted 4–8 and 12–16 weeks after the last treatment session, and then every 8 weeks until loss to follow-up, death or until the end of data collection. Due to the observational nature of the study, reflecting "real-life" management habits, the above timeframes for follow-up visits serve as a

Table 1
Primary endpoints in CIREL.

1. LP-IRI[a] as a first-line treatment:	a. Synchronous mCRC[b] patient b. Metachronous mCRC patient
2. LP-IRI as a consolidation or closing treatment with or without systemic therapy	a. Closing/chemo-holydays: Patient with stable disease under chemo for more than 3 months asking for a chemo break.
3. Intensification of treatment with concomitant systemic therapy	a. Patient with progressive hepatic disease under chemotherapy, naïve to irinotecan b. Patient with progressive extrahepatic disease under chemotherapy, naïve to irinotecan c. Patient with progressive hepatic disease under chemotherapy, including irinotecan d. Patient with progressive extrahepatic disease under chemotherapy, including irinotecan
4. Salvage treatment in progressive patients pre-treated with systemic therapy, with or without concomitant systemic therapy	a. Patient with hepatic progressive disease after failure of three progressive lines of any chemotherapy
5. Combination treatment with ablation with curative intent	
6. Other	

[a] LifePearl microspheres loaded with irinotecan.
[b] metastatic colorectal cancer.

Table 2
Secondary enpoints in CIREL.

Secondary objectives	Outcome measure	Reported by	Measured according to
Safety	Adverse Events and Toxicity	Investigator	CTCAE[c] 4.03
Effectiveness	Overall survival (OS)	Investigator	
	Progression-free survival (PFS)	Independent Central Image Review	RECIST[d] v1.1
	Hepatic progression-free survival (hPFS)	Independent Central Image Review	RECIST v1.1
	Objective Response Rate (ORR)	Independent Central Image Review	RECIST v1.1
	Early tumour shrinkage at ≥20% and ≥30% at first tumour assessment	Independent Central Image Review	RECIST v1.1
	Deepness of response	Independent Central Image Review	RECIST v1.1
	Secondary resection or ablation	Investigator	
Quality of Life	Global health status/QoL[e] score	Patient	EORTC QLQ-C30[f]
	Functional QoL score	Patient	EORTC QLQ-C30
	Symptomatic QoL score	Patient	EORTC QLQ-C30

[c] Common Terminology Criteria for Adverse Events.
[d] Response Evaluation Criteria In Solid Tumors.
[e] Quality of Life.
[f] European Organisation for Research and Treatment of Cancer Quality of Life questionnaire.

guideline for investigators based on suggestions by the CIREL Steering Committee reflecting the usual practice of TACE for this indication in Europe. The patient's treatment and follow-up schedules are solely determined by the treating physician team and should reflect standard of care practice.

1.5. Statistical analysis plan

The observational study will include patients for 30 months and follow-up will terminate once 65% of active patients are deceased. Each patient should be followed-up for as long as possible, and at least for 12 months. An interim analysis after inclusion of 50 patients, focusing on baseline characteristics, feasibility as well as safety and toxicity, is planned. The study aims to enrol up to 150 patients.

The primary endpoint of observed categories of LP-IRI usage will be presented with summary statistics and a 95% Confidence Interval (CI) for the proportions of the categories in Table 1.

Overall Survival (OS), progression-free survival (PFS) and hepatic PFS according to Response Evaluation Criteria In Solid Tumors (RECIST version 1.1) will be plotted by Kaplan-Meier graphs including 95% CIs for median survival. When the final sample has been achieved, a Cox proportional hazards model will be performed to identify covariates associated with different outcomes. Hazard ratios and their 95% CIs will be presented together with p-values. In the analyses of OS, patients will be censored at the last time they were known to be alive. In all analyses according to RECIST criteria, patients will be censored at the last visit when their status was assessed. Patients who died will be regarded as having progressive disease in analyses of PFS and hepatic PFS.

Objective response rate according to RECIST, early tumour shrinkage at ≥20% and ≥30% at first tumour assessment, depth of response (defined as the maximum rate of reduction from the initial tumour burden), and secondary resection or ablation will be presented using summary statistics. At each timepoint, all patients that have data available for determination of an endpoint in the time interval will be included in the summary statistics for that time point. In addition, for the final analysis, a presentation including only patients that have data available at all or a subset of the timepoints will also be given. The time points to include will be based on the available data in order to maximise the number of patients to be included.

Health-related quality of life data will be analysed using version 3 of the EORTC QLQ-C30 Scoring Manual (2001). Data will be presented for the global health status/QoL score, functional and symptom dimensions and for individual items. Since a deterioration of quality of life is expected as the natural course of disease progresses in patients treated with LP-IRI, a bilateral paired sample Student's *t*-test at the 5% level will be used to determine any statistical difference in quality of life from baseline. Further quality of life parameters will be descriptively analysed.

Adverse events (AEs) occurring during the LP-IRI procedure and AEs in the 30 days or more following LP-IRI treatment will be collected (see supplementary Table 1). For each of these, AE summary tables will present:

- The number and grading of AEs
- The number and percentage of subjects with at least one event for AEs

Table 3
Number of enroled centres and patients per country.

Country	Number of centres	Number of patients
Belgium	1	2
Czechia	1	0
France	1	2
Germany	4	19
Greece	1	9
Hungary	1	22
Italy	5	25
Lithuania	1	0
North Macedonia	1	22
Portugal	2	6
Russian Federation	1	2
Spain	4	1

These summaries will be repeated for serious adverse events (SAEs) with CTCAE (Cancer Institute's Common Terminology Criteria for Adverse Events 4.03) grade 3 or 4 and SAEs with CTCAE grade 5.

Above summaries will be repeated for the individual AE categories.

All AEs will be included in listings where the relative day counted from the first administration of LP-IRI treatment (day 1) will be presented together with the relative day counted from the latest administration of LP-IRI treatment.

Laboratory measurements will be presented in summary statistics as both absolute values and change from the baseline with values outside reference ranges flagged in listings. Abnormal laboratory values will be graded according to CTCAE 4.03. and 5.0. All recorded laboratory measurements are listed in supplementary Table 2. A summary table will present the total number of abnormal values and the number of percentage of subjects with at with at least one abnormal value. This summary will be repeated for abnormal values with a CTCAE grade 3 or 4.

2. Discussion

CIREL is the first multicentre, prospective, observational study assessing real-life use of LP-IRI in patients with CRLM and will therefore provide meaningful information about the real-life use as well as safety and effectiveness of LP-IRI.

Since this is a single-device study it will not be possible to extrapolate results to the overall population of CRLM patients treated with TACE. The extent to which data from this study compares to the overall TACE literature will be discussed in the results publication.

As in all observational studies, one challenge will be to assure as complete as possible data collection. To address this, CIREL has implemented a quality system regarding monitoring and data management that will ensure data completeness and correctness. During analyses, care will be taken to describe the amount of missing data and compare patients with missing data and patients with complete data in order to assess potential bias and confounding of results.

Furthermore, particular care must be given to addressing potential selection bias in the study. Patient selection bias is addressed by contractually agreeing with all participating centres that the possibility to participate in the observational study must be presented to all patients that are eligible. In order to assess possible centre selection bias, countries and centres will be compared as far as possible with respect to background characteristics.

At the time of manuscript submission, 23 centres from 12 countries have enroled 110 patients in CIREL (Table 3). The first patient was enroled in February 2018. While data collection was originally foreseen to terminate on 31 January 2022 with up to 500 patients enroled, the CIREL Steering Committee decided to end patient enrolment after 30 months instead of 36 months due to low patient enrolment. Especially the vast amount of studies and trials competing for this patient cohort have resulted in low referral rates for chemoembolisation with LifePearl® Microspheres from multidisciplinary tumour boards.

3. Conclusion

CIREL will analyse data from one of the biggest cohorts of colorectal cancer patients with liver-metastases treated with LifePearl® Microspheres loaded with irinotecan. First interim results are expected to be published in 2020.

Declaration of Competing Interest

Prof. Philippe L. Pereira reports personal fees from Terumo. **Prof. Thomas Helmberger** received speaker honoraria from SIRTEX Medical Europe, **Prof. Dirk Arnold** received consulting fees and speaker honoraria from TERUMO, Boston Scientific, SIRTEX Medical Europe and Biocompatibles. **Prof. Geert Maleux** received speaker fees from SIRTEX Medical Europe. **Prof. Bruno Sangro** has received personal fees from Terumo and BTG, as well as personal fees and a grant from Sirtex Medical. **Anders Nordlund, Phd** has received personal fees from Cardiovascular and Interventional Radiological Society of Europe. **Dr. Ollivier Pellerin** has received personal fees from Merit Medical and shareholdings of COGITh-SAS. **Prof. Julien Taieb** reports receiving honoraria from Merck, Roche, Amgen, Lilly, Sanofi, Samsung, MSD, Servier, Celgene, Pierre Fabre; consulting or advisory Role for Roche, Merck KGaA, Amgen, Lilly, MSD, Servier, Pierre Fabre, Sanofi, Samsung; speakers' Bureau for Servier, Amgen, Roche, Sanofi, Merck, Lilly, Pierre Fabre. **Dr. Fernando Gomez, Prof. Hans Prenen, Dr. Roberto Iezzi, Bleranda Zeka, PhD, Robert Bauer, MA and Nathalie Kaufmann, MSc** report no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2020.05.051.

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