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CLINICAL TRIAL PROTOCOL

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BioPearl™ doxorubicin microspheres for unresectable HCC: a prospective, single-arm, multicenter study: BIOPEARL-ONE

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ABSTRACT

Drug-eluting microsphere transarterial chemoembolization (DEM-TACE) reduces systemic exposure to chemotherapeutic drugs compared with conventional TACE but permanently occludes the embolized vessels, potentially obviating the possibility of re-treatment with TACE. Temporary embolization by resorbable BioPearl™ microspheres might facilitate subsequent re-treatments. We herein describe the trial protocol of BIOPEARL-ONE, a prospective, single-arm, multicenter, post-market clinical follow-up study. The primary objectives are technical success and safety following the use. DEM-TACE with doxorubicin-loaded BioPearl™ for unresectable hepatocellular carcinoma (HCC). The secondary objectives are tumor response, duration of response, progression-free survival, and survival rate at 18 months. Fifty patients with HCC nodules smaller than 5 cm and within the up-to-7 criteria will be enrolled.
Clinical Trial Registration: NCT05911633

PLAIN LANGUAGE SUMMARY

This text describes a clinical study on a new treatment for liver cancer. The treatment uses special drug-coated beads called BioPearl™ microspheres, which temporarily block the blood vessels feeding the tumors. Unlike traditional treatments that permanently block these vessels, these microspheres dissolve over time, potentially allowing for repeated treatments. The study, named BIOPEARL-ONE, is a prospective, single-arm, multicentre, post-market clinical follow-up study. The main goals are to assess the technical success and safety of this treatment. The treatment involves using BioPearl™ microspheres loaded with doxorubicin to treat unresectable hepatocellular carcinoma (HCC). Secondary objectives of the study include evaluating the tumor response, the duration of this response, progression-free survival, and the survival rate at 18 months. The study plans to enroll 50 patients with HCC nodules smaller than 5 cm that meet the "up-to-7" criteria.

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KEYWORDS
Hepatocellular carcinoma; DEM-TACE; doxorubicin; resorbable microsphere; safety; technical success; efficacy

1. Introduction

1.1. Background and rationale

Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers worldwide and is the sixth most common cancer worldwide and the fourth cause of cancer-related death [1,2]. Most newly diagnosed patients are not candidates for curative treatments such as liver transplantation, resection, or ablation, due to advanced tumor stage [3]. However, a significant improvement in overall survival has been observed during the last decade due to the recent developments in locoregional and systemic therapies [4–7].

Transarterial chemoembolization (TACE) is a minimally invasive treatment that cuts off a tumor's blood supply using an embolic agent in combination with local delivery of chemotherapy. During this procedure, a catheter is inserted into the hepatic artery, and a combination of chemotherapeutic drugs (such as doxorubicin or irinotecan) with an embolic agent is delivered directly to the tumor-feeding blood vessels, restricting the tumor blood supply.

The goal of this therapy is to combine the dual effects of embolization and ischemia and high local concentration of chemotherapeutic drug to the tumor. When re-treatment is needed after a first TACE, namely in the case of partial tumor response or stable disease, patent arterial feeders to the tumor will facilitate re-treatment. It will also probably improve efficacy. TACE is , generally, the recommended treatment for intermediate-stage patients (BCLC stage B, defined as multifocal HCC with preserved liver function, no cancer-related symptoms [PS 0], and no vascular invasion or extrahepatic

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Article Highlights

Background and rationale
- Drug-eluting microsphere transarterial chemoembolization (DEM-TACE) is used to reduce systemic exposure to chemotherapeutic drugs but induce permanent occlusion of embolized vessels, which reduces the possibility of subsequent intra-arterial treatments.
- Through their degradation, BioPearl™ microspheres would reopen feeding vessels to allow better access to the lesion for any potential subsequent treatment if required.
- BIOPEARL-ONE is a prospective, single arm, multicenter, post-market clinical follow-up study.

BIOPEARL-ONE study design and eligibility criteria
- BIOPEARL-ONE will recruit adult subjects with HCC nodules <5 cm in largest diameter and within the up-to-7 criteria for which TACE is determined as the best treatment option by a multidisciplinary tumor board.
- All procedural and device-related SAEs and liver-specific SAEs will be followed for up to 18 months and recorded according to CTCAE version 5 at each follow-up visit until disease progression and/or the next treatment option, after which subjects will be followed for survival up to a maximum of 18 months, except for patients that receive a liver transplantation. For those patients, only tumor recurrence in the transplanted liver will need to be reported for up to 18 months.
- Radiological response will be assessed at 4 weeks post-treatment and thereafter trimonthly using the modified response evaluation criteria in solid tumors (mRECIST).

Outcomes measures
- The primary endpoints are to assess: (1) technical success, and (2) the safety of BioPearl™ microspheres loaded with doxorubicin in the treatment of subjects with unresectable HCC.
- The secondary endpoints will provide a preliminary evaluation of the efficacy of BioPearl™ microspheres loaded with doxorubicin: (1) tumor response rate, (2) progression-free survival rate, (3) time to progression (4) duration of response, (5) best response, and (6) survival rate up to 18 months.
- The exploratory endpoints are the measurement of selected biomarker levels (VEGF, IL-6, IL-8, and TNF) and the pharmacokinetic profile of doxorubicin.

Conclusion
- The study aims to demonstrate the feasibility, safety, and preliminary efficacy of BioPearl™ TACE with doxorubicin in patients with HCC. These findings could enhance patient outcomes.

spread), as supported by data from two randomized control trials and a meta-analysis showing significant therapeutic benefit [8–10]. However, BCLC stage B represents a heterogeneous group of patients; not all patients eligible for TACE benefit from it [11,12]. In the 2022 BCLC version, patients are candidates for TACE if they are outside the extended liver transplant criteria but have preserved portal flow and define tumor burden [13]. Moreover, treatment-stage migration is a new concept in the BCLC algorithm allowing TACE as an alternative for (very) early stages when both ablation and liver resection are not feasible for any reason. TACE is also used for down-staging or as a bridging therapy to liver transplantation (LT) to reduce the risk of progression, while the patient is on the waiting list [13–15].

Three TACE techniques are currently used: (1) conventional TACE involves the infusion of chemotherapeutic drugs emulsified in ethiodized oil followed by direct occlusion of the tumor's arterial supply with an embolic agent; (2) DEM-TACE, which uses drug-eluting microspheres onto which cytotoxic drugs, such as doxorubicin, epirubicin, or idarubicin, are loaded through ionic bonds and then slowly released by the microspheres inside the target lesion; and (3) degradable starch microsphere (DSM)-TACE, which also delivers a chemotherapeutic agent inside a target lesion but causes only a temporary occlusion with rapid drug elution depending upon the specific properties of the DSM [16,17]. The microspheres in DSM-TACE do not bind to the chemotherapeutic agent but are mixed with it in a solution, without real loading [18]. The use of microspheres provides some advantages over conventional TACE, as the controlled delivery of the chemotherapeutic agent results in higher local concentrations of the cytotoxic drug inside the tumor while reducing plasma drug levels and therefore potential systemic side effects [16]. DEM-TACE microspheres are characterized by a predictable pharmacokinetic profile of the anticancer agent that allows strict control of the administered dose of the eluted drug [17,18]. Given their small size, DSM can penetrate deeply into the tumor-feeding arteries, assuring less systemic toxicity [19].

Recently, a novel TACE modality combining features of DEM- and DSM-TACE using resorbable DEMs (BioPearl™) was developed. The BioPearl™ microspheres are made using a combination of monomers such as glycerol monomethacrylate, dimethyl acrylamide, and a hydrolytically unstable cross-linker. These components are polymerized together with a sulfopropyl acrylate salt that facilitates the ionic loading of chemotherapeutic drugs. Compared with other drug-eluting microspheres on the market, to the best of our knowledge today, BioPearl™ microspheres are the first temporarily embolic drug-eluting microspheres that can be loaded with chemotherapeutic agents, such as doxorubicin, and release them in a controlled manner. Since BioPearl™ microspheres are resorbable over time, the blood flow to the targeted region can be restored progressively without distorting vascular anatomy including neoangiogenesis or extrahepatic collateral artery formation. Consequently, BioPearl™ microspheres could facilitate re-treatment of the same lesion with TACE if complete response is not achieved.

Here, we present the design of BIOPEARL-ONE, a prospective, single-arm, multicenter study, to assess the safety, technical success, and efficacy of TACE with BioPearl™ microspheres loaded with doxorubicin. This is the first study to clinically evaluate the technical success, safety, and efficacy of TACE with BioPearl™ loaded with doxorubicin.

1.2. Objectives and endpoints

The primary study objectives are to assess (1) the technical success evaluated by the ability to reach near stasis in the treated tumor-feeding arteries during the chemoembolization procedure, and (2) the safety of TACE with BioPearl™ microspheres loaded with doxorubicin in the treatment of subjects with unresectable HCC by reporting all grade 3-4-5 adverse events (AEs) during a period of 4 weeks after the treatment as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5 [20]. Collection and recording of AEs will start from the moment informed consent has been signed, and all inclusion/exclusion criteria have been met until the patient starts survival follow-up. After that, only SAEs related to the device, procedure, or liver will be recorded until 18 months after the initial treatment.

The secondary objective of the study is to evaluate the efficacy of BioPearl™ microspheres loaded with doxorubicin using the following endpoints: (1) tumor response rate (TRR) assessed by mRECIST criteria at 4 weeks and every 3 months; (2) progression-free survival (PFS) defined as time from the treatment to disease progression according to mRECIST criteria or death from any cause, whichever occurs first; (3) time to progression defined as time from treatment to progression according to mRECIST criteria; (4) duration of response according to mRECIST; (5) best response defined as the best response recorded during the study according to mRECIST criteria; and (6) survival rate with follow-up to 18 months. Secondary endpoints will be assessed per local investigator.

Finally, the exploratory objective of the study includes the measurement of serum biomarkers levels (VEGF, IL-6, IL-8 and TNF) at baseline, 24 hours, and day 29 post procedure and the pharmacokinetic profile of doxorubicin (peak plasma concentration (Cmax), area under curve (AUC)) at 5, 10, 20 mins, 1, 2, 4, 6, 8, 24 hours post procedure.

1.3. Trial design

BIOPEARL-ONE is a prospective, single-arm, multi-center study of TACE using BioPearl™ loaded with doxorubicin, aiming to recruit up to 50 evaluable subjects with unresectable HCC. The monitoring in this trial is based on the expectation that TACE-related adverse events (AEs) such as post-embolic syndrome, hepatotoxicity, and liver injuries usually occur during the first 4 post-treatment weeks. Physical examination and laboratory assessments will be performed after 24 hours and at day 29 (±3 days) post-treatment. Four weeks post-treatment imaging will be used, for evaluation of response according to mRECIST and to determine potential liver injuries. Subsequently, all subjects will undergo clinical, biological, and imaging follow-up trimonthly until disease progression and/or they received next treatment line, after which subjects will be followed for survival and safety up to a maximum of 18 months. If indicated, a re-treatment with BioPearl™ microspheres is allowed, and an additional safety follow-up visit will be performed 4 to 6 weeks after the re-treatment. An interval of at least 4 weeks is mandatory between two TACE sessions. Subjects with a treatment and/or device failure or who did not receive treatment for any other reason and subjects who terminate the study before reaching the primary end point will be replaced. The study design is summarized as a flowchart in Figure 1.

2. Methods

2.1. Study setting

The study is sponsored and financially supported by Terumo Europe N.V.

A steering committee has been established with responsibility to guide overall study conduct. An independent Data Monitoring Committee (DMC) will also be established to advise and monitor subject safety.

The trial is to be executed in 10 European hospitals based in four different countries. BIOPEARL-ONE study was approved by the local ethics committees and is being conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guideline (Table 1). The maximum number of subjects per investigation site is 12, i.e., 24% of the total population to avoid a potential bias caused by an overrepresentation of a single investigation site in terms of the number of subjects.

2.2. Eligibility criteria

BIOPEARL-ONE will recruit adult subjects with HCC nodules <5 cm in the longest axis and within the up-to-7 criteria for which TACE is determined as the best treatment option by a multidisciplinary tumor board [13]. Eligibility criteria are provided in Table 2.

2.3. Study procedures

All participants will provide written informed consent for the study prior to the performance of study-related procedures or the collection of study-related data. A screening visit will take place during the 4 weeks prior to TACE. The baseline contrast-enhanced MRI scan of the abdomen should not be older than 4 weeks prior to the consent date. Contrast-enhanced CT abdomen is only allowed in case MRI is contraindicated. Throughout the study, the same imaging modality should be used. A contrast enhanced CT scan of the chest, abdomen, and pelvic region will also be performed at baseline to confirm the diagnosis and exclude extrahepatic spread.

BioPearl™ microspheres are delivered as a sterile lyophilized powder and need to be reconstituted in aqueous saline as specified in the instructions for use to reach an approximate size of 200 µm, after which they can be loaded with doxorubicin. The injected dose of doxorubicin used will be recorded. The use of an occlusive micro-balloon catheter will not be allowed. The microcatheter will be introduced into the target vessel according to standard techniques, positioning the catheter tip as close as possible to the treatment site to avoid inadvertent occlusion of normal vessels. BioPearl™ microspheres will be slowly injected to reach the near stasis of the feeders. Additional bland embolization with unloaded BioPearl™ microsphere injection can be performed to reach near stasis after injection of the total volume of BioPearl™ loaded with doxorubicin. No other embolic agent will be used in this study, either alone or as a supplement to the procedure. The total volume injected (inclusive of BioPearl™ microspheres loaded with doxorubicin, contrast, and water; and bland BioPearl™ microspheres, if applicable) will be recorded. If the patient requires repeated TACE to obtain the best response, and there are no contraindications, further chemoembolization can be performed using BioPearl™ microspheres.

Laboratory tests will be conducted before discharge and at day 29 post procedure and trimonthly thereafter until 18 months post procedure. For the subjects participating in the pharmacokinetic profile evaluation, additional blood samples will be collected at 5, 10, and 20 minutes and at 1, 2, 4, 6, 8, and 24 hours after the

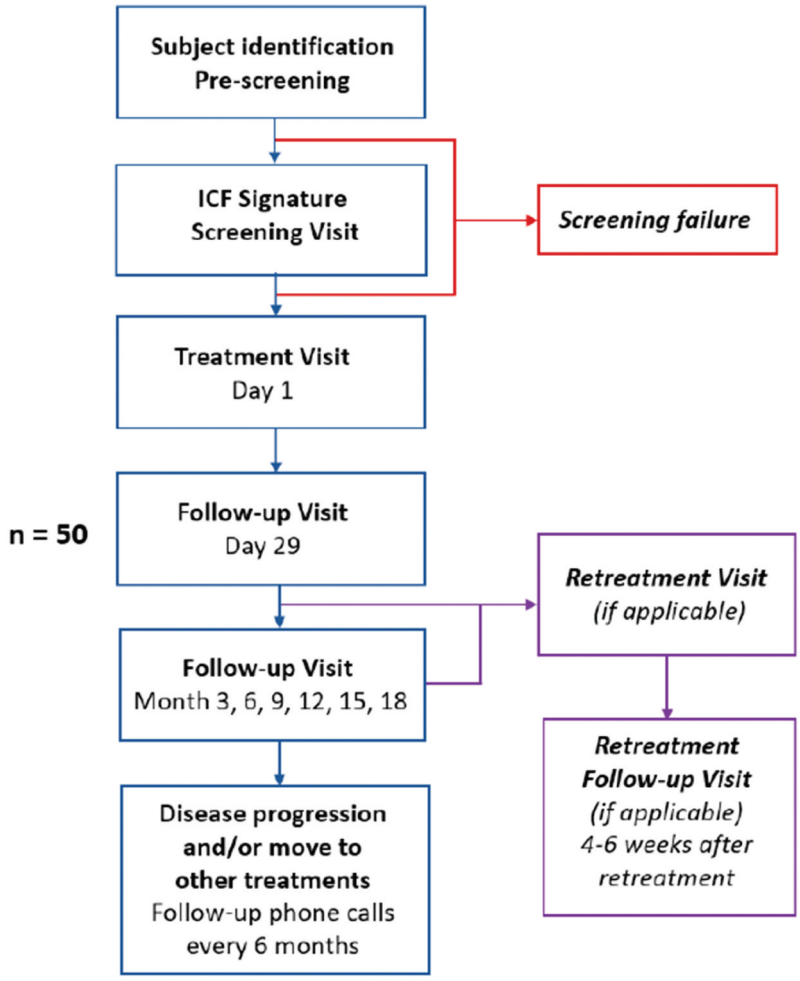

Figure 1. Study flowchart.

Table 1. List of ethics committees.

Countries	Ethics committees/Approval number
Belgium	FAMHP/CIV-23-07-043650–RS01-SM01/1327857
France	ANSM/2024-A01201-46 CPP/224 D08
Germany	Landesärztekammer (LAK)/F-2023-097#A1
Italy	CET Lombardia 4/INT 201/23

procedure. For these patients, serum VEGF, IL-6, IL-8, and TNF concentrations will be quantified by ELISA at baseline, after 24 hours, and at day 29 post-treatment.

2.4. Outcomes

The first assessment of response and possible liver injuries by imaging will be performed at day 29 after TACE and trimonthly until 18 months after the initial TACE treatment.

Toxicity events will be recorded according to CTCAE version 5 at each follow-up visit, and ongoing AEs will be followed up until resolution or stabilization and at time of early discontinuation. All subjects will undergo clinical follow-up until disease progression and/or next treatment, after which subjects will be followed for survival and safety up to a maximum of 18 months.

2.5. Recruitment and participant timeline

The estimated recruitment period will be approximately 3 years until 50 subjects have been enrolled and treated, without treatment or device failure.

Each subject is followed up for a maximum of 18 months. Once the disease progresses inside the liver with no possibility for further TACE treatment and/or if the subject is moved to a next treatment, survival follow-up visits/calls will occur every 6 months until death or month 18. A survival follow-up visit is not required if the subject completed the follow-up visit at month 18.

The end of the study will coincide with the last visit of the last subject.

A subject's participation in a study may be terminated early for medical reasons, incomplete follow-up, or voluntary withdrawal, after which the patient will be followed according to the institution's standard care.

2.6. Data collection methods and data management

An electronic Case Report Form (eCRF) is developed using an Electronic Data Capture (EDC) system. To ensure data quality, validation, and consistency, edit checks will be designed

Table 2. Eligibility criteria.

Inclusion criteria	Exclusion criteria
1. Subject is at least 18 years old 2. Subject with HCC confirmed by histology or according to the latest applicable version of the EASL criteria 3. Subject with tumor(s) < 5 cm and within the up to 7 criteria: the sum of the diameter of the largest tumor (in cm) and the number of tumors must be ≤ 7 4. BCLC B subject or BCLC A subject not a candidate for curative treatment at the time of study inclusion or who has failed/recurred after resection/ablation. Recurrence in the segment of RFA is not allowed 5. WHO or ECOG performance status 0 or 1 6. Subject deemed treatable in one session for initial treatment. 7. Normal liver or compensated cirrhosis with preserved liver function (Child-Pugh Class A) 8. Total bilirubin ≤2.0 mg/dl 9. Adequate bone marrow function: Hemoglobin ≥9 g/dl, absolute neutrophil count ≥ 1.0 × 109/L, platelet count ≥ 75 × 109/L 10. Subject with no ascites or with minor ascites controlled by sodium dietary restrictions (subject receiving diuretic treatment or paracentesis is not eligible) 11. Adequate renal function (serum creatinine < 1.5 X ULN) 12. Subject has provided written informed consent 13. Subjects of childbearing/reproductive potential should use adequate birth control measures, during the study treatment period until survival follow up	1. Subject previously treated with any systemic therapy for HCC 2. Subject previously treated with intra-arterial loco-regional therapy for HCC 3. Eligible for curative treatment at the time of study inclusion 4. Recurrence in the segment of a prior thermal ablation 5. Advanced liver disease: Child-Pugh's B-C class or active gastrointestinal bleeding, encephalopathy 6. Advanced tumoral disease: BCLC class C or D (vascular invasion – even segmental, extra-hepatic spread or cancer-related symptoms performance status > 1) 7. History of another primary tumor. Exceptions include: 1) Malignancy treated with curative intent ≥5 years before inclusion and with no known active disease 2) Malignancy which occurred <5 years before, not active and not expected to recur or be clinically relevant in the next 5 years 8. Subject with history of biliary tree disease or biliary dilatation 9. Portal vein thrombosis, porto-systemic shunt, hepatofugal blood flow or absent portal blood flow in the liver area to be treated 10. Contraindication to multiphasic CT and MRI (e.g., allergy to contrast media) 11. Any other contraindication for embolization procedure or Doxorubicin treatment 12. Subject is currently participating in an investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the current study endpoints Note: Trials requiring extended follow-up for products that were investigational, but have become commercially available since then, are not considered investigational trials 13. In the Investigator's opinion subject has (a) co-morbid condition(s) that could limit the subject's ability to participate in the study, compliance with follow-up requirements or impact the scientific integrity of the study 14. Pregnant or breast-feeding woman

during EDC system development. An audit trail logging all data entered and edited will be available within the EDC system.

2.7. Statistical methods

2.7.1. Sample size

The planned sample size is based on regulatory requirements. A total of 50 subjects will provide sufficient precision around the estimated proportion of subjects with any grade 3 to 5 procedure/device related adverse event and estimated proportion of subjects with technical success.

2.7.2. Endpoints

Co-primary endpoints and secondary efficacy endpoints will be analyzed based on the intention-to-treat analysis set, i.e., enrolled subjects for whom treatment with BioPearl™ was attempted on study day 1. Sensitivity analyses excluding patients with any major protocol deviations may also be presented.

The *co-primary endpoints*, proportion of subjects with any severe (CTCAE V5.0 grade 3 to 5) procedure or device-related adverse event during the 4-week period after initial treatment and proportion of subjects with technical success at initial treatment will be summarized together with an exact two-sided 95% confidence interval.

For the co-primary endpoint analyses, all subjects included in the intention-to-treat analysis set (i.e., enrolled subjects for whom treatment with BioPearl™ was attempted on day 1) will be included in the denominator for the co-primary endpoints: proportion of subjects with any grade 3 to 5 procedure or study device related, treatment-emergent adverse event during the 4-week period after initial treatment as well as proportion of subjects with technical success at initial treatment (day 1).

The proportion of subjects with a *complete/partial response, stable disease and progressive disease* will be summarized by visit. The proportion of subjects with a *best response* over time of complete/partial response, stable disease and progressive disease will also be summarized.

Kaplan–Meier estimates for the median *time to progression or death from any cause* and the proportion of subjects remaining progression-free and surviving at 18 months will be presented. Kaplan–Meier estimates for the median *time to progression* and the proportion of subjects remaining progression-free at 18 months will also be presented. Kaplan–Meier estimates for the median *duration of response* and the proportion of responders with a durable response of ≥6 months will be presented. Kaplan–Meier estimates for the median *survival time* and the proportion of subjects surviving at 18 months will also be presented.

2.7.3. Subsequent re-treatment(s) with Biopearl™

Subsequent re-treatment(s) with Biopearl™ may be administered for reasons other than progression, and the requirement for re-treatment is not unexpected. Subjects will continue to be followed up for progression after re-treatment.

Evaluation of time to progression or death from any cause will be assessed from study day 1, initial treatment session, irrespective of whether re-treatment sessions were required. A swimmer plot will be presented providing a visual presentation of the time to progression or death from any cause and the timing of any re-treatment sessions for each subject. Subjects will be color-coded by number of treatment sessions with Biopearl™ to enable a visual inspection of the relationship between time to progression or death from any cause

and the number of treatments with Biopearl™. Kaplan–Meier plots of progression-free survival time by number of treatments with Biopearl™ may be presented post-hoc as appropriate to further evaluate the relationship between time to progression or death from any cause and number of treatments with Biopearl™.

2.7.4. Subsequent alternative treatments

Subsequent alternative treatments may be administered for reasons other than progression, and not unexpected given subjects are receiving a locoregional study treatment. Subjects receiving subsequent alternative treatment will enter survival follow-up.

Kaplan–Meier estimates for the median time to progression or death from any cause and the proportion of subjects remaining progression-free and surviving at 18 months will be presented. The handling of subjects receiving subsequent alternative treatment will be as follows:

- Subjects who have not progressed prior to the start of subsequent alternative treatment/survival follow-up and have not died at the time of the analysis will be censored at the time of their latest available response assessment prior to entering survival follow-up.
- Subjects who start subsequent alternative treatment and enter survival follow-up prior to any response assessment will be censored at study day 1 unless death occurred prior to the day 29.
- Subjects who have not progressed prior to the start of subsequent alternative treatment/survival follow-up and die after two or more missed response assessment visits (due to entering survival follow-up) will be censored at the time of their last available response assessment prior to entering survival follow-up.

3. Conclusion

Since the publication of two RCTs and a subsequent meta-analysis [8–10] demonstrating that the survival benefits of TACE are superior to the best supportive care, TACE has become the standard of care for intermediate stage (BCLC-B) HCC [8–10]. In recent publications, the median overall survival with TACE ranges from 19 to 38 months [21–27].

In this era of effective systemic therapies using combinations of immune checkpoint inhibitors and anti-angiogenic molecules, the role and the expected outcomes of TACE have been refined [5–7]. Indeed, in the updated version of the BCLC algorithm, based on "treatment stage migration "the indication of TACE is extended to (very) early-stage HCC as an alternative option when curative treatments are not feasible. For intermediate stages, TACE indication is restricted to the subgroup of HCC patients with well-defined tumor burden and preserved portal flow accessible to selective treatment [13]. Downstaging with TACE has become a reliable method for selecting patients for LT, as the tumor response to locoregional treatment has been suggested as a valuable indicator of tumor biological activity [14,15].

These recent changes in HCC management have led to modifications in how TACE is administered. Indeed, TACE is increasingly delivered in the most selective manner possible to obtain the best tumor response while sparing the non-tumor liver parenchyma and thus preserving liver function.

The effectiveness of TACE in achieving complete tumor necrosis has considerably increased other year, driven by the evolution of the adopted procedure modality. The super selective procedure was more often associated with complete tumor necrosis. It also means that viable tumor cells may remain in the peripheral region [28].

Allowing recanalization of tumor feeders that could be favored by resorbable embolics might be of great value when a subsequent TACE is needed to treat the remaining tumoral tissue. This is, however, not always the case after a TACE procedure when profound ischemia occurs, and no subsequent recanalization of the arteries happens. When tumor feeders or hepatic arteries remain occluded, it can jeopardize subsequent TACE and other intra-arterial therapies, thus changing the line of therapy toward systemic treatments. Compared with other drug-eluting microspheres on the market, BioPearl™ are the only temporarily embolic drug-eluting microspheres that can be loaded with and release chemotherapeutic agents, such as doxorubicin, in a controlled manner. Since BioPearl™ microspheres are resorbable over time, the blood flow to the targeted region can be progressively restored. In animal models, BioPearl™ degradation begins upon implantation, with partial degradation of microspheres observed at 4-week assessment, and increased blood flow to the target site is observed as early as 2 weeks following implantation. Consequently, BioPearl™ microspheres will probably facilitate subsequent treatment of the same lesion with TACE if a complete response is not achieved after the first treatment.

In summary, BIOPEARL-ONE will be the first study to investigate the technical success, safety, and preliminary efficacy of BioPearl™ microspheres loaded with doxorubicin for TACE in patients with unresectable HCC. A good safety profile will warrant additional investigations evaluating the benefit of repeated BioPearl™ TACE to demonstrate a potential higher response rate and improvement in survival outcomes.

Author contribution statement

G Verset and G Maleux were responsive for the study concept and design. G Verset drafted the manuscript. All authors were involved in the critical revision of the manuscript. G Verset, R Iezzi, and G Maleux supervised the study in collaboration with the sponsor.

Disclosure statement

G Verset is a consultant for Terumo, R Iezzi has received honoraria for lectures from Terumo, IGEA, Betaglue, Medtronic, I Bargellini is a consultant for Terumo, Boston-Scientific, P Pereira has received honoraria for lectures, expert testimony, or advisory board from Medtronic, C Spreafico is a consultant for Terumo and Boston-Scientific.

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The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Ethical declaration

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

BIOPEARL-ONE study was approved by the local ethics committees (see below) and is being conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Ethical committee names and approval numbers

Belgium

- FAMHP/CIV-23-07-043650–RS01-SM01/1327857

France

- ANSM/2024-A01201-46
- CPP/224 D08

Germany

- Landesärztekammer (LAK)/F-2023-097#A1

Italy

- CET Lombardia 4/INT 201/23

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Data availability statement

The study documents including the subject data from EDC will be stored electronically in the Sponsor's eTMF system. The retention period of study documents for this study is 15 years after the last product has been placed in the market according to MDR 2017/745, Annex IX Chapter III.

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   • **This study presents relevant data for our research.**
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