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STUDY PROTOCOL INTERVENTIONAL ONCOLOGY

Evaluating the Effectiveness of Yttrium-90 Glass Microspheres in the Treatment of Hepatocellular Carcinoma, Intrahepatic Cholangiocarcinoma, and Metastatic Colorectal Cancer in Practice: Protocol for the Prospective PROACTIF Phase IV Registry Study in France

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Abstract

Primary Objective Recently, selective internal radiation therapy using yttrium-90 (Y90) glass microspheres (TheraSphere™) was approved for reimbursement by health authorities in France. The PROACTIF study aims to gather data on effectiveness, patient quality of life, and safety with use of Y90 glass microspheres in real-world clinical settings in France.

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Inclusion Criteria Patient with a diagnosis of hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (iCC), and/or metastatic colorectal cancer (mCRC) who was treated with a dose of Y90 glass microspheres that has been reimbursed in France and who do not oppose use of their personal medical data.
Exclusion Criteria If data collection is opposed, treatment is reimbursed but not administered, or treatment is administered but not reimbursed.
Outcome Measures Primary outcome measures include overall survival from time of Y90 glass microsphere treatment and quality of life, as assessed using the Functional Assessment of Cancer Therapy- Hepatobiliary questionnaire.
Estimated Number of Patients to Be Included This is an open study and there is no set number of patients; 115 have already been enrolled.
Planned Subgroup Analyses Analyses will be stratified by disease state (HCC, iCC, or mCRC). Subgroups to be analyzed include age group, unilobar/bilobar disease at baseline, Eastern Cooperative Oncology Group (ECOG) status at baseline, liver tumor burden at baseline, target lesion size, and standard versus multi-compartment personalized dosimetry treatment.
Planned Recruitment and Observation Period Recruitment includes patients who are prescribed and treated with a commercial vial of Y90 glass microspheres between 01 January 2019 and 31 December 2024.
Trial registration ClinicalTrials.gov Identifier: NCT04069468.

Keywords Selective internal radiation therapy · Hepatocellular carcinoma · Intrahepatic cholangiocarcinoma · Liver metastatic colorectal cancer · Yttrium-90

Abbreviations

HCC	Hepatocellular carcinoma
iCC	Intrahepatic cholangiocarcinoma
mCRC	Metastatic colorectal cancer
SIRT	Selective internal radiation therapy
BCLC	Barcelona clinic liver cancer
Y90	Yttrium-90
PROACTIF	A prospective, post approval, multiple centre, open-label, non- interventional, registry study to evaluate effectiveness of therasphere in clinical practice in France
QoL	Quality of life
RIHP3	Recherche impliquant la personne humaine de categorie 3
FACT-Hep	Functional assessment of cancer therapy – hepatobiliary cancer
Bq	Becquerel
EDC	Electronic data capture
PIS	Patient information sheet
GDPR	General data protection regulation
eCRF	Electronic case report form
PVT	Portal vein thrombosis
^{99m}Tc-MAA	Technetium albumin aggregated
SPECT	Single-photon emission computed tomography
CT	Computed tomography
IFU	Instructions for use
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
INR	International normalized ratio
AFP	Alpha-fetoprotein
CA19-9	Carbohydrate antigen 19-9
CEA	Carcinoembryonic antigen
MRI	Magnetic resonance imaging
RECIST 1.1	Response evaluation criteria in solid tumors
mRECIST	Modified response evaluation criteria in solid tumors
MCD	Multi-compartment dosimetry
PET	Positron emission tomography
OS	Overall survival
SAEs	Serious adverse events
AEs	Adverse events
NCI-CTCAE	National cancer institute common terminology criteria for adverse events
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease
DVH	Dose volume histogram
ECOG	Eastern cooperative oncology group
ALBI	Albumin-bilirubin
CI	Confidence interval
FOLFOX	Folinic acid, fluorouracil, and oxaliplatin

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Introduction

Current treatment paradigms for patients with unresectable hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (iCC), and metastatic colorectal cancer (mCRC) often include local treatments, locoregional therapies (mainly intra-arterial), or systemic agents. Systemic therapies used in the treatment of HCC may include sorafenib, regorafenib, lenvatinib, and emerging combinations of these and other systemic drugs such as the recent atezolizumab + bevacizumab combination. Locoregional therapies aside of intraarterial treatments, often used include various forms of ablation [1–4]. Treatment options and sequencing vary significantly for liver tumors based upon whether they are of primary or metastatic origin, as detailed in the National Comprehensive Cancer Network (NCCN) guidelines.[5, 6] Depending on an individual patient's disease characteristics (i.e., disease stage, performance status, liver function), these treatments may sometimes be able to serve as a bridge to transplantation or resection.[7, 4, 8, 9].

Selective internal radiation therapy (SIRT) is a locoregional treatment option that is used for patients with primary or secondary liver tumors. SIRT involves the administration of radioactive microspheres into the tumor through the tumor vasculature to deliver targeted radiation therapy directly to malignant tissue. Benefits of SIRT for patients include reduced toxicities and preservation of quality of life (QoL) as compared to other treatments for patients with nonresectable disease. [10, 11, 12] SIRT is not currently part of the Barcelona Clinic Liver Cancer (BCLC) treatment algorithm for HCC, as positive randomized phase III trials are needed to support its integration. However, there is a large body of literature documenting the safety and efficacy of radioactive microspheres when used in the standard of care clinical practice.[13, 14, 15, 16, 12] Specifically, there is over 20 years' worth of data supporting the use of TheraSphere™ Yttrium-90 (Y90) glass microspheres in the treatment of HCC for early to advanced disease, including the recent LEGACY study, which served as the basis for approval in the United States, and the recent positive guidance from the United Kingdom's National Institute for Health and Care Excellence [17, 18, 19, 20, 14, 21, 22, 23, 24, 25]. Additionally, there is a growing body of evidence demonstrating the utility of Y-90 glass microspheres in the treatment of liver metastases, including the recently published EPOCH clinical trial, which combined systemic therapy with SIRT in patients with liver-dominant mCRC [26–31].

In early 2019, a "positive recommendation" was issued in France for reimbursement of Y90 glass microspheres for HCC for a trial period of 5 years (through 2024); in early 2020, this recommendation for reimbursable use was expanded to include iCC and mCRC to the liver for an additional 4-year trial period (through 2024). These decisions were issued by the Haute Autorité de Santé – Commission Nationale d'évaluations des dispositifs médicaux et des Technologies de Santé (HAS-CNEDiMTS). A post-market clinical follow-up study was requested by the French health authorities to support the continuation of the reimbursement after the initial 5-year period.

To that end, a registry was developed and is being maintained to monitor effectiveness of treatment (A **Pro**spective, Post-**A**pproval, Multiple Centre, Open-Label, Non-Interventional, Registry Study to Evaluate Effe**c**tiveness of **T**heraSphere in Cl**i**nical Practice in **F**rance, or PROACTIF). PROACTIF includes approximately 30 sites across France. The aggregation of high-quality data from multiple sites across multiple malignancies presents a unique opportunity to study Y90 glass microspheres in clinical practice and could support inclusion of SIRT into BCLC treatment algorithm and into European and US guidelines for HCC and iCC. The primary objective of PROACTIF is to gather data on effectiveness, patient quality of life (QoL), and safety with use of Y90 glass microspheres in real-world clinical settings in France. In this manuscript, we detail the research protocol of the PROACTIF study.

Study Design

PROACTIF is a prospective registry of the clinical use of Glass Y90 microsphere for the treatment of liver malignancies in France. This study was classified in France as *Recherche Impliquant la Personne Humaine de Catégorie 3* (RIHP 3) by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), this is an observational, non-interventional study. The protocol was assigned by the French National Commission for Research Involving Human Persons (CNRIPH) for review to an Independent Ethics Committee prior to the study's initiation (French Ethics Committee « Ile de France VII») and approved by this committee. The study is registered at ClinicalTrials.gov (NCT04069468).

Inclusion/Exclusion Criteria

Inclusion Criteria: The registry includes patients with a diagnosis of HCC, mCRC, or iCC for whom a commercial dose of Y90 glass microspheres has been/will be administered between 01 January 2019 and 31 December 2024, and who do not oppose use of their personal medical data (verbal consent). All data generated during patient visits conducted as part of local standard medical practices will

Cells in Grey: Assessment must be performed within 14 days of pre-TheraSphere™ angiography

		TheraSphere™ Treatment				Follow Up Visits	Final Visit	Follow Up Visits After 12 Months
		Day 1 First Treatment		Day 28 Second Treatment (if needed)		Follow-Up Visits Every 2-4 Months	12 Months Post Initial Treatment/ Time of Withdrawal	At Routine/ Standard of Care Follow-Up Visits Until Study Close
	Patient Registration	Visit 2a		Visit 2b				
Data or Assessment Recorded	Baseline/ Visit 1	Pre-TS	TS	Pre-TS	TS			
Patient Enrollment								
Information to Patient, Documentation of non-opposition to data collection, eligibility[1]	X							
Enrollment, Patient registration and Identification (ID, partial date of birth)	X							
Compliance to HAS requirement and to TheraSphere™ Treatment requirement	X							
Documentation of TheraSphere™ contraindication	←	→						
Patient characteristics (gender, BMI/weight, main comorbidities[2])	←	→						
Set treatment goal/expectation	←	→						
Quality of Life Questionnaire (FACT-Hep)	←	→						
ECOG Performance Status	←	—	—	—	→		X *(if possible)*	X *(if possible)*
Disease Characteristics								
Liver disease description[3]	←	→						
Liver cancer history[4]	←	→						
CT or MRI (tumor characteristics[5])	←	→						
PVT description[6]	←	→		X		X		
Liver function score and tumor score								
Ascites/Encephalopathy	←	→		X		←	→	
Child Pugh Score	←	→		X		←	→	
BCLC Stage	←	→				←	→	
Laboratory tests								
Biochemistry-coagulation (Albumin, Bilirubin, AST, ALT, INR, Prothrombin Ratio or PT), including ALBI score derivation, creatinine	←	—	—	—	—	—	→	
Tumor markers (AFP, CA 19-9, CEA)	←	→				←	→	
TheraSphere™ Treatment parameters								
Pre-TheraSphere™ angiography[7], coils placement, ^{99m}Tc-MAA administration		X		X				
^{99m}Tc-MAA SPECT or SPECT/CT imaging		X		X				
TheraSphere™ Administration[8]			X		X			
Y90 SPECT/CT, PET/CT, or PET/MRI imaging[9]			X		X			
Dosimetry: liver/tumor fractions, calculation of absorbed dose to the tumor, perfused liver, non-tumoral liver and lung[10]		←	—	—	→			
Treatment Follow-Up								
Treatment expectation met[11], qualitative response assessment[12]	←	→				X		
Subsequent anti-cancer treatment[12]							←	→
Study withdrawal[13]							X	
Survival[15]						←	—	→
Adverse Events								
SAEs		←	—	—	→			X
AEs grade 3 or higher related to device or device procedure[16]		←	—	—	→			

Abbreviations: ID = identification; HAS = Haute Autorité de Santé; BMI = body mass index; FACT-Hep = Functional Assessment of Cancer Therapy – Hepatobiliary; ECOG = Eastern Cooperative Oncology Group; CT = computed tomography; MRI = magnetic resonance imaging; PVT = portal vein thrombosis; BCLC = Barcelona Clinic Liver Cancer; AST = aspartate aminotransferase; ALT = alanine aminotransferase; INR = international normalized ratio; PT = prothrombin time; ALBI = albumin bilirubin; AFP = alpha-fetoprotein; CA 19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; ^{99m}Tc-MAA = Technetium-99m Macroaggregated Albumin; SPECT = single-photon emission computed tomography; PET = positron emission tomography; SAE = serious adverse events; AE = adverse event

Fig. 1 SPIRIT flow diagram for the PROACTIF study

be included in the registry (Fig. 1). Participating sites and investigators are listed in Supplementary Material 1. Eligibility and conditions for reimbursement for patients with HCC, iCC, and mCRC are detailed in Table 1.

Exclusion Criteria: If the patient is reimbursed, treatment is administered, and data collection is opposed, only information about the patient's eligibility will be documented. Similarly, if Y90 glass microsphere treatment is ordered but not administered, only patient eligibility and end-of-study data are collected (Fig. 2).

Procedure

All treatment planning and procedures will be performed according to each site's institutional procedures and in accordance with the Instructions for Use (IFU) included with Y90 glass microspheres. The investigator should

Table 1 Inclusion and exclusion criteria for the PROACTIF Registry for patients with hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and metastatic colorectal cancer

	Hepatocellular carcinoma	Intrahepatic cholangiocarcinoma	Metastatic colorectal cancer
Inclusion criteria (conditions for reimbursement)	1. Confirmed HCC, by histology or America Association for the Study of Liver Diseases (AASLD) or EASL imaging criteria	1. Confirmed iCC	1. Confirmed mCRC
	2. Patient scheduled to receive TherasSphere treatment per Multi-disciplinary Tumor Board (MTB) decision	2.Patient scheduled to receive TherasSphere treatment per MTB decision	2. Patient scheduled to receive TherasSphere treatment per MTB decision
	3. Treatment given as a palliative intent (patient not eligible* for resection or ablation)	3. First line palliative treatment for iCC	3. Preserved general health condition (ECOG score ≤ 2)
	4. Patient who is BCLC B or BCLC C or with PVT**	4. Patient unresectable at diagnosis or in a recurrence after resection	4. Hepatic tumor load ($< 25\%$)
	5. Patient who is not eligible* for, or has failed sorafenib treatment	5. With or without association with chemotherapy	5. Absence of extrahepatic disease (except in situ primary colorectal cancer)
	6. Patient with good general status (ECOG score 0 or 1)	6. Preserved general health condition (ECOG ≤ 1) when treated with TheraSphere with concomitant chemotherapy	6. Refractory or intolerant to all approved intra venous and oral therapies for colorectal cancer. Progression under chemotherapy should be documented
	7. Patient with preserved liver function*** (Child Pugh A-B)	7. Preserved general health condition (ECOG score ≤ 2) when treated with TheraSphere alone	
		8. Absence of extrahepatic disease	
		9. Hepatic tumor load $< 50\%$	
		10. Patient with preserved liver function (Child–Pugh score A or B in case of cirrhosis)	
Exclusion criteria	1. Have refused data collection; and/or		
	2. Will not receive reimbursement for their TheraSphere treatment		

*Treatment not recommended by the MTB or contra indicated or has failed or was not tolerated

**Portal vein invasion by tumor

***Preserved liver function: includes patients with different degrees of liver functional reserve (non-treated liver) that has to be carefully evaluated. Compensated liver disease (without ascites) is required to obtain optimal outcome. (Forner et al. 2018; EASL Guidelines 2018)

document the expected treatment outcome (i.e., partial/complete response, disease control, improvement of disease symptoms, improvement of portal vein thrombosis (PVT), and downstaging to resection). Baseline data on disease presentation will be collected, including type of tumoral portal thrombus, location of the portal vein thrombosis, and whether the thrombus is present in the hepatic vein. Pre-treatment procedures will include administration of technetium macroaggregated albumin (^{99m}Tc-MAA) and imaging (^{99m}Tc-MAA single-photon emission computed tomography [SPECT] or SPECT/computed tomography [CT]) to ensure the absence of extrahepatic deposition of Y90 glass microspheres, coiling of aberrant arteries (if appropriate), and evaluation of lung shunting. ^{99m}Tc-MAA SPECT or SPECT/CT should be used also to determine appropriate dosimetry to the tumor and liver normal tissue. Laboratory tests will be conducted as part of routine institutional practice for each malignancy, and should include alanine aminotransferase (ALT), aspartate aminotransferase (AST), international normalized ratio (INR), albumin, bilirubin, creatinine, and tumor markers (alpha-fetoprotein [AFP], carbohydrate antigen 19-9 [CA 19-9], carcinoembryonic antigen [CEA]). QoL data will be collected at baseline, prior to, and after treatment. Pre- and post-treatment imaging assessments will be conducted as part of routine institutional practice for each malignancy; this should include pre-treatment imaging (CT or magnetic resonance imaging [MRI]) with appropriate description of tumor number, location, and target and non-target evaluation according to Response

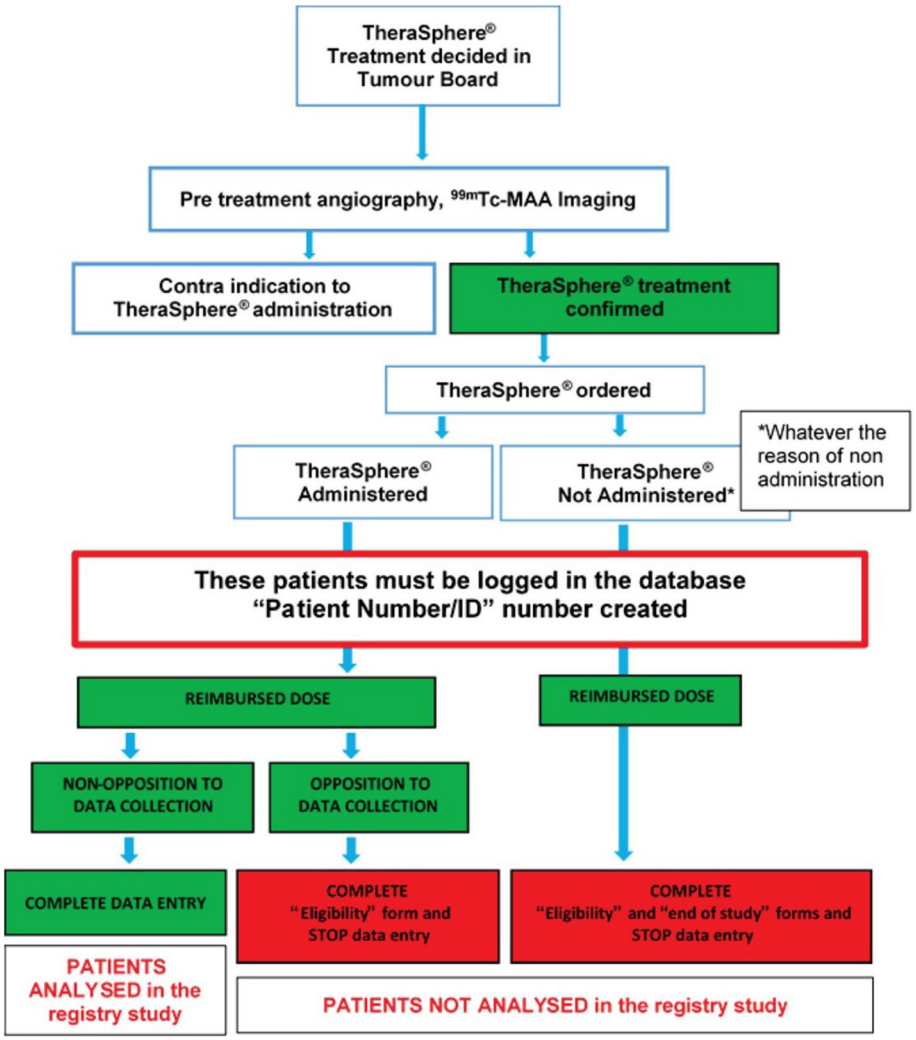

Fig. 2 TheraSphere Registry recruitment process

Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) and modified Response Evaluation Criteria in Solid Tumors (mRECIST).

Data on dosimetry will be collected as part of the registry database for all patients. Multi-compartment personalized dosimetry (MCD) will be performed whenever possible for HCC and iCC and will rely on dosimetry software (e.g., Simplicit^{90}Y^{TM} [Mirada Medical]) to calculate tumor and non-tumor absorbed doses. For centers that do not have access to dosimetry software, such software (Simplicit^{90}Y^{TM}) will be provided free of charge by the study sponsors for the duration of the study, along with appropriate training. In addition, dosimetry guidance for threshold tumor absorbed dose and perfused liver, all normal liver absorbed dose are providing in the protocol based on data on dose/response and outcome and dose/toxicity known threshold [32–36].

Initial local reads of imaging and dosimetry will be completed by the site radiophysicist and nuclear medicine physician. A central read of dosimetry by an experienced central reviewer is planned for patients with HCC and iCC; therefore, pre-treatment CT or MRI, ^{99m}Tc-MAA SPECT or SPECT/CT and post-Y90 glass microsphere administration imaging (Y-90 PET) will be uploaded to a central imaging data base. The reviewer is unblinded, and will receive information regarding previous treatment, treated lesion location, activity administered, and location of the administration; the reviewer will not have access to the patient's record itself or information beyond what has been listed. Central reads will be completed only for HCC and iCC due to the recommendation for personalized dosimetry in these patients; as single-compartment dosimetry is recommended for mCRC, central reads will not be completed for these patients.

Y90 glass microsphere infusion can either be selective (tumor feeding artery, liver segment, or specific liver sector) or non-selective (whole liver, left or right liver). Depending on the mapped vasculature of the patient and the biological distribution of the target tumor, treatment may be done in one or in a series of infusions. If multiple

treatments are needed, the first session will typically focus on the area of the liver with the greatest tumor burden. After completion of the first treatment, a second ^{99m}Tc-MAA SPECT or SPECT/CT could be performed to confirm or update treatment plans if the second treatment will be greater than 1 month after the initial mapping; the aim of this is to ensure that the lung shunt evaluation and dosimetry evaluation are still accurate. Second treatments will typically take place 30–45 days after the initial treatment.

Follow-Up Protocol

Post-Y90 glass microsphere treatment will be conducted per site standards; treatment follow-up data will be gathered at the routine follow-up visit for each patient along with QoL data (Fig. 1). Follow-up visits will be conducted every 2–4 months post-Y90 glass microsphere treatment until 12 months post-treatment; after 12 months, follow-up visits will be performed per local practice standards. Laboratory tests should include ALT, AST, INR, albumin, bilirubin, creatinine, and tumor markers (AFP, CA 19-9, CEA). Imaging follow-up should include CT or MRI with the local qualitative evaluation of target lesion and overall response, method of imaging, and evaluation results, which should be documented using RECIST 1.1 and mRECIST. Additionally, investigators should document if the expected treatment goal was reached. Additionally, treatment data involving systemic therapy is collected throughout the study period, including type of treatment, duration of treatment, and indication for treatment. After the first 12 months of follow-up after the final Y90 glass microsphere administration, only QoL and survival status will be collected at each follow-up visit. If follow-up treatment is conducted outside of the treatment center, efforts will be made to gather these data from the patient's home institution. Data collection will be stopped if the patient withdraws their non-opposition to data collection status, starts another anti-cancer treatment, receives best supportive care, or follow-up is no longer possible.

If the patient withdraws from the data collection, the date and reason for withdrawal will be documented. Patient survival status (alive or dead) and subsequent anti-cancer treatment received (type and start/stop dates) will be documented at interim analysis points and at study end date; these data will be entered by study sites. If the patient is lost to follow-up, the principal investigator at the site will attempt to re-contact the patient at least twice before the patient is deemed lost to follow-up, in this situation survival status will be collected at the study closure date by contacted the patient GP or the civil status registry.

Outcome Measures

Primary outcomes are defined as follows:

(1) Overall Survival: defined as time from start of Y90 glass microsphere treatment until date of death from any cause or study end date.
(2) Quality-of-Life assessment: determined by the administration of the FACT-Hep Questionnaire before and after treatment [37].

Secondary outcomes are defined as follows:

(1) Serious Adverse Events (SAEs) of any cause graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI-CTCAE v 5.0) [38].
(2) Grade 3 or Higher Adverse Events (AEs) related or possibly related to the device or the device administration procedure that occur up to 90 days after treatment or the first follow-up visit (if after 90 days post-treatment), graded using NCI-CTCAE v. 5.0.
(3) Re-Hospitalizations: number and duration of re-hospitalizations related to Y90 glass microsphere treatment up to 30 days after the first administration of Y90 glass microsphere treatment.
(4) Treatment Expectation: based upon the description of the treatment expectation (e.g., survival, disease control) before Y90 glass microsphere treatment, and number of patients achieving their treatment expectations.
(5) Qualitative Tumor Response Assessment: will be conducted for both the index lesion and overall response. Defined as the number of patients having achieved a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) using either RECIST 1.1 or mRECIST.
(6) Target tumor marker response, defined as a $\geq$ 50% decrease in:
    a. AFP levels for patients with a baseline AFP level $\geq$ 200 ng/mL;
    b. CA 19-9 levels for patients with a baseline CA 19-9 level greater than or equal to twice the upper limit of normal; and/or
    c. CEA levels for patients with a baseline CEA level greater than or equal to twice the upper limit of normal.
(7) Post-Y90 glass microsphere anti-cancer treatment; includes both the number of patients receiving such treatment and type of treatment.
(8) Post-Y90 glass microsphere best supportive care, if no follow-up is no longer possible or if follow-up was interrupted by investigator decision.

9) Vascular access: description of vascular access (radial or femoral) used to administer Y90 glass microspheres.

Additionally, specific outcomes related to dosimetry will be collected; these are detailed in Supplementary Material 2.

Planned Subgroup Analyses

All analyses will be performed according to the disease indication (HCC, iCC, and mCRC). The "treated population" for analysis will include all patients within each disease type who were prescribed, received, and reimbursed for Y90 glass microsphere treatment, and who have not opposed collection of their data as part of this study. The "dosimetry population" for analysis will include all patients for whom dosimetry data are available within each disease type. All analyses will be performed on the "treated population" for each disease, save for the dosimetry analyses. Additional analyses may be performed on several subgroups of interest. For each of the three disease types, the following subgroup analyses may be conducted:

- Age group ($\geq$ 18 to $<$ 65 years, $\geq$ 65 to $<$ 75 years, $\geq$ 75 years)
- Unilobar or bilobar disease at baseline
- Eastern Cooperative Oncology Group (ECOG) status (0, $>$ 0) at baseline
- Albumin/bilirubin (ALBI) score (1 or 2, 3) at baseline
- Liver tumor burden at baseline ($<$ 25%, $\geq$ 25%)
- Target lesion size ($\leq$ 5 cm vs $>$ 5 cm, $\leq$ 7 cm vs. $>$ 7 cm, $\leq$ 10 cm vs. $>$ 10 cm)
- Selective versus non-selective (lobar or whole liver) administration
- Standard versus multi-compartment personalized dosimetry treatment

Additional Analyses for Each Disease Type are Summarized in Table 2

Statistical Methods to be Applied Effectiveness Analyses: All effectiveness analyses will utilize the treated population. Kaplan–Meier analysis will be used for OS, and median OS will be computed along with a 95% confidence interval (CI). Kaplan–Meier will also be used for time to deterioration of QoL. To assess the impact of subgroup factors detailed earlier, univariate and multivariate Cox Proportional Hazards analyses will be performed. The number of patients achieving their treatment expectations will be summarized. Similarly, tumor marker response and qualitative tumor response will also be reported. Univariate and multivariate logistic regression analyses of binary effectiveness points (i.e., achievement of treatment expectation, tumor marker response, and qualitative tumor response) will also be performed to assess the impact of the afore mentioned subgroup factors.

Safety Analyses: Incidence of AEs (Grade 3 or higher) and SAEs will be calculated according to the Medical Dictionary for Regulatory Activities [39]. Descriptive

Table 2 Subgroup analyses for each malignancy type in the PROACTIF registry study

Hepatocellular carcinoma	Intrahepatic cholangiocarcinoma	Metastatic colorectal cancer
•Etiology of underlying disease	•Prior resection (Yes, No)	•CEA ($<$ 2×ULN, $\geq$ 2×ULN) at baseline
•Child Pugh score (A or B) at baseline for cirrhotic patients	•CA 19-9 ($<$ 2xULN, $\geq$ 2xULN) at baseline	•Previous line of systemic chemotherapy ($\leq$ 2, $>$ 2)
•Cirrhosis versus no cirrhosis	•Cirrhosis versus no cirrhosis	•Prior local or/and locoregional treatment (Yes, No)
•Prior TACE treatment (Yes, No)	•Concomitant chemotherapy versus non concomitant chemotherapy	•Concomitant chemotherapy versus non concomitant chemotherapy
•PVT classification (PVT 1, PVT 2, PVT 3, PVT 4) at baseline	•Threshold absorbed doses to the tumor $<$ 205 Gy, 205–250 Gy, $>$ 250 Gy (by local and central assessment)	•Threshold absorbed doses to the tumor $<$ 100 and $\geq$ 100 Gy (by local assessment)
•BCLC stage (B, C) at baseline		
•Prior systemic treatment, including sorafenib (Yes, No)		
•AFP ($<$ 200 ng/ml, $\geq$ 200 ng/mL, $<$ 400 ng/mL, $\geq$ 400 ng/mL) at baseline		
•Threshold absorbed doses to the tumor $\geq$ 205, $<$ 205 Gy and $\geq$ 250, $<$ 250 Gy (by local and central assessment)		

summaries of laboratory results will be presented by study visit; these will include changes from baseline. Number of re-hospitalizations due to Y90 glass microsphere treatment as well as length of re-hospitalizations will be summarized.

Treatment Targeting and Dosimetry Analyses: All dosimetry analyses will utilize the dosimetry population. For the treatment targeting description, the following will be cross-tabulated and summarized as numbers and percentages for local assessments (all indications) and central assessments (HCC and iCC):

- Location of tumor(s) at baseline and locations of lesions targeted by ^{99m}Tc-MAA using ^{99m}Tc-MAA SPECT or SPECT/CT;
- Location of tumor(s) at baseline and location of lesions targeted by Y-90 using Y-90 PET/CT, Y-90 PET/MRI, or Y-90 SPECT/CT;
- Location of tumor(s) targeted by ^{99m}Tc-MAA based on ^{99m}Tc-MAA (SPECT or SPECT/CT) and location of tumor targeted by Y-90 using post-treatment PET/CT, PET/MRI, or SPECT/CT; and
- PVT at baseline and PVT targeted by ^{99m}Tc-MAA (using ^{99m}Tc-MAA SPECT or SPECT/CT) and Y-90 (using Y-90 PET/CT, PET/MRI, or SPECT/CT), when applicable.

For dosimetry-specific outcomes, the following the following will be cross-tabulated and summarized for local assessments (all indications) and central assessments (HCC and iCC):

- Pre-treatment and post-treatment volume and absorbed dose determined for total perfused tumor, index lesion, perfused normal tissue and whole liver normal tissue using 99mTc-MAA (SPECT or SPECT/CT) and Y-90 (PET/CT or PET/MRI), when applicable.
- DVH for total perfused tumor, index lesion and whole normal liver tissue, using 99mTc-MAA (SPECT or SPECT/CT) and Y-90 (PET/CT or PET/MRI), when applicable.

Additional details regarding planned regression analyses of dosimetry data can be found in Supplementary Material 3.

Quality of Life Analyses: QoL scores will be calculated for each domain and each item at each time point; differences from baseline will be summarized. A "deterioration in QoL" is defined as a 7-point decrease in the total score or death, whichever comes first. The time to deterioration in QoL will be calculated as the interval between the date of first Y90 glass microsphere treatment and deterioration in QoL. If a patient is lost to follow-up the patient will be considered to be a "death" in the time-to-deterioration analysis. The Kaplan–Meier method will be used.

Interim and Final Analyses: Planned interim analyses will be conducted 1, 2, and 4 years into the overall study. Final analyses will be performed after the 5 years of enrollment and one additional year of follow-up is completed; the registry will close 1 year after the final patient receives Y90 glass microsphere treatment so as to ensure follow-up data for that individual, therefore in 2025. The first interim analysis will only include patients with HCC, as the registry was begun prior to the addition of the iCC and mCRC indications.

Discussion

The PROACTIF study was designed to collect real-world data of the use of Y90 glass microspheres in the treatment of primary and secondary liver tumors in France. An extrinsic goal of the study is to provide these data in response to a request from HAS-CNEDMiTS, which requested such follow-up after its 5-year approval for reimbursement; we believe this will help to ensure patients in France continue to have access to this treatment.

More broadly, however, the study will provide data on patient outcomes in the context of real-world cancer care for HCC, iCC, and mCRC, particularly in conjunction with other concurrent treatment options, These data will include variables that will be critical in informing treatment decision-making in the future, including the diversity of patient selection, disease presentation, treatment procedures, treatment effectiveness (including, but not restricted to, survival), safety, QoL, and dosimetry. Additionally, the hope is to help equip hospitals in France to expand the use of multicompartment/personalized dosimetry, which has been shown to yield better outcomes in select HCC patients. Finally, we believe that the results from this registry could support the inclusion of SIRT with Y90 glass microspheres in the BCLC treatment algorithm for HCC, as well as in the European and US guidelines for the treatment of mCRC and iCC.

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Declarations

Conflict of interest E.G.: Received fees and a grant from BTG Ltd./ Boston Scientific Corporation. J.P.: Nothing to disclose. C.B.: Nothing to disclose. C.S.: Nothing to disclose. D.M-G.: Nothing to disclose. J.E.: Received fees and support for research from Boston Scientific; consultant for Roche, AstraZeneca, MSD, BMS, Eisai, Bayer, and Ipsen. J-F.B: Consultant for Bayer, Astra-Zeneca, IPSEN, ESAI, Roche, and BMS. A.B.: Nothing to disclose. J.T.: Nothing to disclose. A.R: Nothing to disclose. S.B.: Nothing to disclose. D.S.: Nothing to disclose. T. de B.: Consultant for Boston Scientific Corporation, Guerbet, GE-Healthcare, HD Technologies, Terumo, AstraZeneca, and Eisai; speaker for Boston Scientific Corporation, Guerbet, GE-Healthcare, HD Technologies, and Terumo. C. S-D: Nothing to disclose. C.M.: Nothing to disclose. J.G.: Nothing to disclose. P.C.: Nothing to disclose. H.R.: Consultant for Boston Scientific Corporation. E.V.: Received fees for methodological consulting from Biocompatibles UK Ltd. S.M.: Nothing to disclose. E.V.: Receives fees from Bayer, BMS, Johnson & Johnson, and Boston Scientific Corporation; serves as consultant for Nanobiotix; academic collaboration with EchoSens, Fluoptics, and IntraSence. B.P.: Employee of Biocompatibles/Boston Scientific Corporation. E.B.: Employee of Biocompatibles/Boston Scientific Corporation. B.G.: Consultant for Boston Scientific, Quantum Surgical, Terumo. Received research grant from Roche, Guerbet.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was classified in France as Recherche Impliquant la Personne Humaine de Catégorie 3 (RIHP 3) by the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) due to its observational, non-interventional design. The protocol was approved by a randomly assigned to one of the 39 Independent Ethics Committees in France prior to the study's initiation (assigned to French Ethics Committee « Ile de France VII»); assignments are made by the French National Commission for Research Involving Human Persons (CNRIPH).

Informed Consent Patients will receive a Patient Information Sheet (PIS), which they will be able to review prior to treatment and about which patients will be given the opportunity to ask questions of the investigator or delegate. As detailed by the General Data Protection Regulation (GDPR) and requested by the ethics committee, this PIS will inform the patient about the purpose and aim of the registry and how their personal medical data will be used. After reviewing this sheet, clinicians will document whether the patient expresses verbal non-opposition to data collection in the patient's record ("non-opposition to data collection").

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

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