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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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1 **Title:** Evaluating the Effectiveness of TheraSphere Yttrium-90 Glass Microspheres in the Treatment
2 of Hepatocellular Carcinoma, Intrahepatic Cholangiocarcinoma, and Metastatic Colorectal Cancer in
3 Practice: Protocol for the PROACTIF Phase IV Study

4 **Running Title:** Yttrium-90 Glass Microspheres in Current Clinical Use

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61 Corporation. The funding body provided support in the analysis of data and in providing
62 medical writing support for the manuscript.
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65 Corporation.

66 J.P.: Nothing to disclose.

67 C.B.: Nothing to disclose.

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90 Fluoptics, and IntraSence.

91 B.P.: Employee of Biocompatibles/Boston Scientific Corporation.

92 E.B.: Employee of Biocompatibles/Boston Scientific Corporation.

93 B.G.: Consultant for Boston Scientific, Quantum Surgical, Terumo. Received research grant
94 from Roche, Guerbet.

95 **3. Ethical Approval:** All procedures performed in studies involving human participants were
96 in accordance with the ethical standards of the institutional and/or national research
97 committee and with the 1964 Helsinki declaration and its later amendments or comparable
98 ethical standards.

99

100 This study was classified in France as Recherche Impliquant la Personne Humaine de
101 Catégorie 3 (RIHP 3) by the Agence Nationale de Sécurité du Médicament et des Produits
102 de Santé (ANSM) due to its observational, non-interventional design. The protocol was
103 approved by a randomly assigned to one of the 39 Independent Ethics Committees in France
104 prior to the study's initiation (assigned to French Ethics Committee « Ile de France VII ») ;
105 assignments are made by the French National Commission for Research Involving Human
106 Persons (CNRIPH).

107

108 **4. Informed Consent:** Patients will receive a Patient Information Sheet (PIS), which they will
109 be able to review prior to treatment and about which patients will be given the opportunity
110 to ask questions of the investigator or delegate. As detailed by the General Data Protection
111 Regulation (GDPR) and requested by the ethics committee, this PIS will inform the patient

112 about the purpose and aim of the registry and how their personal medical data will be used.
113 After reviewing this sheet, clinicians will document whether the patient expresses verbal
114 non-opposition to data collection in the patient's record ("non-opposition to data
115 collection").

116

117 **5. Consent for publication:** Consent for publication was obtained for every individual
118 person's data included in the study.

119

121 **Title:** Evaluating the Effectiveness of Yttrium-90 Glass Microspheres in the Treatment of
122 Hepatocellular Carcinoma, Intrahepatic Cholangiocarcinoma, and Metastatic Colorectal Cancer in
123 Practice: Protocol for the PROACTIF Phase IV Study

124 **Running Title:** Yttrium-90 Glass Microspheres in Current Clinical Use

125

126 **ABSTRACT**

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

131 **Inclusion Criteria:** Patient with a diagnosis of hepatocellular carcinoma (HCC), intrahepatic
132 cholangiocarcinoma (iCC), and/or metastatic colorectal cancer (mCRC) who was treated with a dose
133 of Y90 glass microspheres that has been reimbursed in France and who do not oppose use of their
134 personal medical data.

135 **Exclusion Criteria:** If data collection is opposed, treatment is reimbursed but not administered, or
136 treatment is administered but not reimbursed.

137 **Outcome Measures:** Primary outcome measures include overall survival from time of Y90 glass
138 microsphere treatment and quality of life, as assessed using the Functional Assessment of Cancer
139 Therapy- Hepatobiliary questionnaire.

140 **Estimated Number of Patients to Be Included:** This is an open study and there is no set number of
141 patients; 115 have already been enrolled.

142 **Planned Subgroup Analyses:** Analyses will be stratified by disease state (HCC, iCC, or mCRC).
143 Subgroups to be analyzed include age group, unilobar/bilobar disease at baseline, Eastern
144 Cooperative Oncology Group (ECOG) status at baseline, liver tumor burden at baseline, target lesion
145 size, and standard versus multi-compartment personalized dosimetry treatment.

146 **Planned Recruitment and Observation Period:** Recruitment includes patients who are prescribed
147 and treated with a commercial vial of Y90 glass microspheres between 01 January 2019 and 31
148 December 2024.

149 **Key Words:** selective internal radiation therapy; hepatocellular carcinoma; intrahepatic
150 cholangiocarcinoma; liver metastatic colorectal cancer; yttrium-90

151

152

153 **INTRODUCTION**

154 Current treatment paradigms for patients with unresectable hepatocellular carcinoma (HCC),
155 intrahepatic cholangiocarcinoma (iCC), and metastatic colorectal cancer (mCRC) often include local
156 treatments, locoregional therapies (mainly intra-arterial), or systemic agents. Systemic therapies used
157 in the treatment of HCC may include sorafenib, regorafenib, lenvatinib, and emerging combinations
158 of these and other systemic drugs such as the recent atezolizumab + bevacizumab combination.
159 Locoregional therapies aside of intraarterial treatments, often used include various forms of
160 ablation.[10-13] Treatment options and sequencing vary significantly for liver tumors based upon
161 whether they are of primary or metastatic origin, as detailed in the National Comprehensive Cancer
162 Network (NCCN) guidelines.[2; 3] Depending on an individual patient’s disease characteristics (i.e.,
163 disease stage, performance status, liver function), these treatments may sometimes be able to serve
164 as a bridge to transplantation or resection.[4; 13; 14; 28]

165 Selective internal radiation therapy (SIRT) is a locoregional treatment option that is used for patients
166 with primary or secondary liver tumors. SIRT involves the administration of radioactive
167 microspheres into the tumor through the tumor vasculature to deliver targeted radiation therapy
168 directly to malignant tissue. Benefits of SIRT for patients include reduced toxicities and preservation
169 of quality of life (QoL) as compared to other treatments for patients with nonresectable disease. [9;
170 35; 39] SIRT is not currently part of the Barcelona Clinic Liver Cancer (BCLC) treatment algorithm
171 for HCC, as positive randomized phase III trials are needed to support its integration. However, there
172 is a large body of literature documenting the safety and efficacy of radioactive microspheres when
173 used in the standard of care clinical practice.[1; 26; 37-39] Specifically, there is over 20 years’ worth
174 of data supporting the use of TheraSphere™ Yttrium-90 (Y90) glass microspheres in the treatment
175 of HCC for early to advanced disease, including the recent LEGACY study, which served as the basis

176 for approval in the United States, and the recent positive guidance from the United Kingdom’s
177 National Institute for Health and Care Excellence.[6; 21-23; 26; 27; 29; 31; 34; 36] Additionally,
178 there is a growing body of evidence demonstrating the utility of Y-90 glass microspheres in the
179 treatment of liver metastases, including the recently published EPOCH clinical trial, which combined
180 systemic therapy with SIRT in patients with liver-dominant mCRC.[7; 19; 24; 25; 32; 33]

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

188 To that end, a registry was developed and is being maintained to monitor effectiveness of treatment
189 (A **P**rospective, Post-**A**pproval, Multiple Centre, Open-Label, Non-Interventional, Registry Study to
190 Evaluate **E**ffectiveness of **T**heraSpheres in **C**linical Practice in **F**rance, or PROACTIF). PROACTIF
191 includes approximately 30 sites across France. The aggregation of high-quality data from multiple
192 sites across multiple malignancies presents a unique opportunity to study Y90 glass microspheres in
193 clinical practice and could support inclusion of SIRT into BCLC treatment algorithm and into
194 European and US guidelines for HCC and iCC. The primary objective of PROACTIF is to gather
195 data on effectiveness, patient quality of life (QoL), and safety with use of Y90 glass microspheres in
196 real-world clinical settings in France. In this manuscript, we detail the research protocol of the
197 PROACTIF study.

198 **STUDY DESIGN**

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

207 **Inclusion/Exclusion Criteria**

208 Inclusion Criteria: The registry includes patients with a diagnosis of HCC, mCRC, or iCC for whom
209 a commercial dose of Y90 glass microspheres has been/will be administered between 01 January
210 2019 and 31 December 2024, and who do not oppose use of their personal medical data (verbal
211 consent). All data generated during patient visits conducted as part of local standard medical practices
212 will be included in the registry (Figure 1). Participating sites and investigators are listed in
213 Supplementary Material 1. Eligibility and conditions for reimbursement for patients with HCC, iCC,
214 and mCRC are detailed in Table 1.

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

219

220

221 **Procedure**

222 All treatment planning and procedures will be performed according to each site's institutional
223 procedures and in accordance with the Instructions for Use (IFU) included with Y90 glass
224 microspheres. The investigator should document the expected treatment outcome (i.e.
225 partial/complete response, disease control, improvement of disease symptoms, improvement of portal
226 vein thrombosis (PVT), and downstaging to resection). Baseline data on disease presentation will be
227 collected, including type of tumoral portal thrombus, location of the portal vein thrombosis, and
228 whether the thrombus is present in the hepatic vein. Pre-treatment procedures will include
229 administration of technetium macroaggregated albumin (^{99m}Tc -MAA) and imaging (^{99m}Tc -MAA
230 single-photon emission computed tomography [SPECT] or SPECT/computed tomography [CT]) to
231 ensure the absence of extrahepatic deposition of Y90 glass microspheres, coiling of aberrant arteries
232 (if appropriate), and evaluation of lung shunting. ^{99m}Tc -MAA SPECT or SPECT/CT should be used
233 also to determine appropriate dosimetry to the tumor and liver normal tissue. Laboratory tests will be
234 conducted as part of routine institutional practice for each malignancy, and should include alanine
235 aminotransferase (ALT), aspartate aminotransferase (AST), international normalized ratio (INR),
236 albumin, bilirubin, creatinine, and tumor markers (alpha-fetoprotein [AFP], carbohydrate antigen 19-
237 9 [CA 19-9], carcinoembryonic antigen [CEA]). QoL data will be collected at baseline, prior to, and
238 after treatment. Pre- and post-treatment imaging assessments will be conducted as part of routine
239 institutional practice for each malignancy; this should include pre-treatment imaging (CT or magnetic
240 resonance imaging [MRI]) with appropriate description of tumor number, location, and target and
241 non-target evaluation according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1)
242 and modified Response Evaluation Criteria in Solid Tumors (mRECIST).

243 Data on dosimetry will be collected as part of the registry database for all patients. Multi-
244 compartment personalized dosimetry (MCD) will be performed whenever possible for HCC and iCC
245 and will rely on dosimetry software (e.g., Simplicit⁹⁰YTM [Mirada Medical]) to calculate tumor and
246 non-tumor absorbed doses. For centers that do not have access to dosimetry software, such software
247 (Simplicit⁹⁰YTM) will be provided free of charge by the study sponsors for the duration of the study,
248 along with appropriate training. In addition, dosimetry guidance for threshold tumor absorbed dose
249 and perfused liver, all normal liver absorbed dose are providing in the protocol based on data on
250 dose/response and outcome and dose/toxicity known threshold [8; 15-18]

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

261 Y90 glass microsphere infusion can either be selective (tumor feeding artery, liver segment, or
262 specific liver sector) or non-selective (whole liver, left or right liver). Depending on the mapped
263 vasculature of the patient and the biological distribution of the target tumor, treatment may be done
264 in one or in a series of infusions. If multiple treatments are needed, the first session will typically
265 focus on the area of the liver with the greatest tumor burden. After completion of the first treatment,

266 a second ^{99m}Tc-MAA SPECT or SPECT/CT could be performed to confirm or update treatment plans
267 if the second treatment will be greater than one month after the initial mapping; the aim of this is to
268 ensure that the lung shunt evaluation and dosimetry evaluation are still accurate. Second treatments
269 will typically take place 30-45 days after the initial treatment.

270

271 **Follow-Up Protocol**

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

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

295

296 **Outcome Measures**

297 Primary outcomes are defined as follows:

- 298 1) Overall Survival: defined as time from start of Y90 glass microsphere treatment until date of
299 death from any cause or study end date.
- 300 2) Quality-of-Life assessment: determined by the administration of the FACT-Hep
301 Questionnaire before and after treatment.[5]

302 Secondary outcomes are defined as follows:

- 303 1) Serious Adverse Events (SAEs) of any cause graded using the National Cancer Institute
304 Common Terminology Criteria for Adverse Events, version 5.0 (NCI-CTCAE v 5.0).[20]
- 305 2) Grade 3 or Higher Adverse Events (AEs) related or possibly related to the device or the device
306 administration procedure that occur up to 90 days after treatment or the first follow-up visit
307 (if after 90 days post-treatment), graded using NCI-CTCAE v. 5.0.

- 308 3) Re-Hospitalizations: number and duration of re-hospitalizations related to Y90 glass
309 microsphere treatment up to 30 days after the first administration of Y90 glass microsphere
310 treatment.
- 311 4) Treatment Expectation: based upon the description of the treatment expectation (e.g. survival,
312 disease control) before Y90 glass microsphere treatment, and number of patients achieving
313 their treatment expectations.
- 314 5) Qualitative Tumor Response Assessment: will be conducted for both the index lesion and
315 overall response. Defined as the number of patients having achieved a complete response
316 (CR), partial response (PR), stable disease (SD), or progressive disease (PD) using either
317 RECIST 1.1 or mRECIST.
- 318 6) Target tumor marker response, defined as a $\geq 50\%$ decrease in:
- 319 a. AFP levels for patients with a baseline AFP level $\geq 200\text{ng/mL}$;
- 320 b. CA 19-9 levels for patients with a baseline CA 19-9 level greater than or equal to
321 twice the upper limit of normal; and/or
- 322 c. CEA levels for patients with a baseline CEA level greater than or equal to twice the
323 upper limit of normal.
- 324 7) Post-Y90 glass microsphere anti-cancer treatment; includes both the number of patients
325 receiving such treatment and type of treatment.
- 326 8) Post-Y90 glass microsphere best supportive care, if no follow-up is no longer possible or if
327 follow-up was interrupted by investigator decision.
- 328 9) Vascular access: description of vascular access (radial or femoral) used to administer Y90
329 glass microspheres.

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

332

333 *Planned Subgroup Analyses*

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

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

350 **Additional analyses for each disease type are summarized in Table 2.**

351

352 Statistical Methods to Be Applied

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

362

363 Safety Analyses: Incidence of AEs (Grade 3 or higher) and SAEs will be calculated according to the
364 Medical Dictionary for Regulatory Activities.[30] Descriptive summaries of laboratory results will
365 be presented by study visit; these will include changes from baseline. Number of re-hospitalizations
366 due to Y90 glass microsphere treatment as well as length of re-hospitalizations will be summarized

367

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

- 372
- Location of tumor(s) at baseline and locations of lesions targeted by ^{99m}Tc -MAA using ^{99m}Tc -
373 MAA SPECT or SPECT/CT;

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

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

- 383 • Pre-treatment and post treatment volume and absorbed dose determined for total perfused
384 tumor, index lesion, perfused normal tissue and whole liver normal tissue using ^{99m}Tc-MAA
385 (SPECT or SPECT/CT) and Y-90 (PET/CT or PET/MRI), when applicable.
- 386 • DVH for total perfused tumor, index lesion and whole normal liver tissue, using ^{99m}Tc-MAA
387 (SPECT or SPECT/CT) and Y-90 (PET/CT or PET/MRI), when applicable.

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

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

396

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

403

404 **DISCUSSION**

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

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

420

421 **ABBREVIATIONS**

Abbreviation	Definition
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 <u>P</u> rospective, <u>P</u> ost <u>A</u> pproval, <u>M</u> ultiple Centre, <u>O</u> pen-Label, <u>N</u> on- <u>I</u> nterventional, <u>R</u> egistry Study to Evaluate Effectiveness of <u>T</u> heraSphere in <u>C</u> linical Practice in <u>F</u> rance
QoL	Quality of life
RIHP3	Recherche Impliquant la Personne Humaine de Catégorie 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	Multicompartment 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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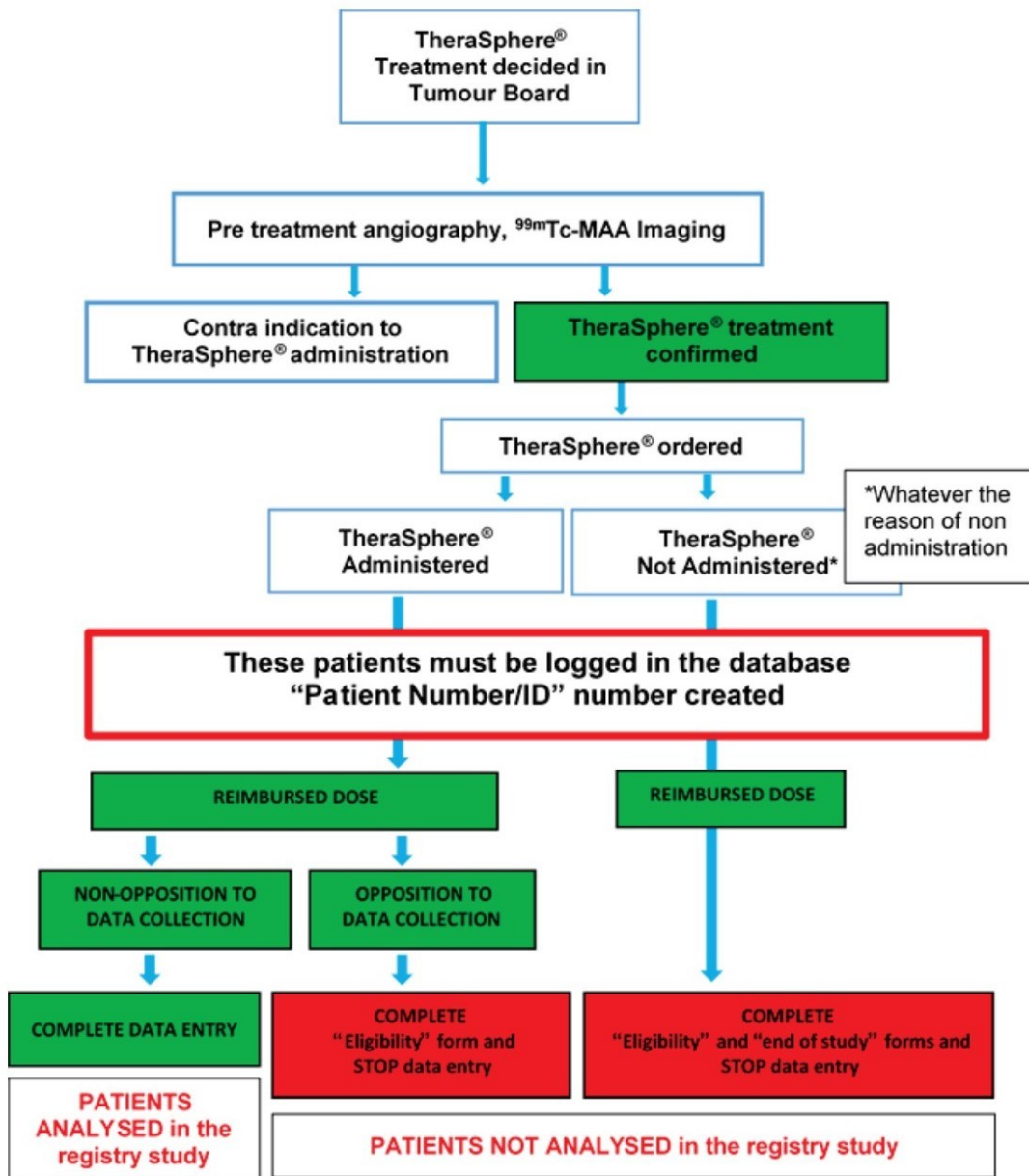
535 **Figures.**

536 **Figure 1.** SPIRIT flow diagram for the PROACTIF study.

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

Data or Assessment Recorded	TheraSphere™ Treatment					Follow Up Visits Every 2-4 Months	Final Visit 12 Months Post Initial Treatment/ Time of Withdrawal	Follow Up Visits After 12 Months At Routine/ Standard of Care Follow-Up Visits Until Study Close
	Patient Registration	Day 1 First Treatment		Day 28 Second Treatment (if needed)				
	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								

538 **Figure 2.** TheraSphere Registry recruitment process.



539

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

	Hepatocellular Carcinoma	Intrahepatic Cholangiocarcinoma	Metastatic Colorectal Cancer
Inclusion Criteria (conditions for reimbursement)	<ol style="list-style-type: none"> 1. Confirmed HCC, by histology or America Association for the Study of Liver Diseases (AASLD) or EASL imaging criteria 2. Patient scheduled to receive TherasSphere treatment per Multi-disciplinary Tumour Board (MTB) decision 3. Treatment given as a palliative intent (patient not eligible* for resection or ablation) 4. Patient who is BCLC B or BCLC C or with PVT** 5. Patient who is not eligible* for, or has failed sorafenib treatment 6. Patient with good general status (ECOG score 0 or 1) 7. Patient with preserved liver function*** (Child Pugh A-B) 	<ol style="list-style-type: none"> 1. Confirmed iCC 2. Patient scheduled to receive TherasSphere treatment per MTB decision 3. First line palliative treatment for iCC 4. Patient unresectable at diagnosis or in a recurrence after resection 5. With or without association with chemotherapy 6. Preserved general health condition (ECOG \leq 1) when treated with TheraSphere with concomitant chemotherapy 7. Preserved general health condition (ECOG score \leq 2) when treated with TheraSphere alone 8. Absence of extrahepatic disease 9. Hepatic tumour load <50% 10. Patient with preserved liver function (Child-Pugh score A or B in case of cirrhosis) 	<ol style="list-style-type: none"> 1. Confirmed mCRC 2. Patient scheduled to receive TherasSphere treatment per MTB decision 3. Preserved general health condition (ECOG score \leq 2). 4. Hepatic tumour load (<25%) 5. Absence of extrahepatic disease (except in situ primary colorectal cancer) 6. Refractory or intolerant to all approved intra venous and oral therapies for colorectal cancer. Progression under chemotherapy should be documented
Exclusion Criteria	<ol style="list-style-type: none"> 1. Have refused data collection; and/or 2. Will not receive reimbursement for their TheraSphere treatment. 		

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

543 ** Portal vein invasion by tumor

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

547

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

Hepatocellular Carcinoma	Intrahepatic Cholangiocarcinoma	Metastatic Colorectal Cancer
<ul style="list-style-type: none"> • Etiology of underlying disease • Child Pugh score (A or B) at baseline for cirrhotic patients • Cirrhosis versus no cirrhosis • Prior TACE treatment (Yes, No) • PVT classification (PVT 1, PVT 2, PVT 3, PVT 4) at baseline • BCLC stage (B, C) at baseline • Prior systemic treatment, including sorafenib (Yes, No) • AFP (<200 ng/ml, ≥200 ng/mL, <400ng/mL, ≥400 ng/mL) at baseline • Threshold absorbed doses to the tumour ≥ 205, < 205 Gy and ≥250, <250 Gy (by local and central assessment) 	<ul style="list-style-type: none"> • Prior resection (Yes, No) • CA 19-9 (<2xULN, ≥ 2xULN) at baseline • Cirrhosis versus no cirrhosis • Concomitant chemotherapy versus non concomitant chemotherapy • Threshold absorbed doses to the tumour < 205 Gy, 205-250 Gy, >250 Gy (by local and central assessment) 	<ul style="list-style-type: none"> • CEA (<2xULN, ≥ 2xULN) at baseline • Previous line of systemic chemotherapy (≤ 2, >2) • Prior local or/and locoregional treatment (Yes, No) • Concomitant chemotherapy versus non concomitant chemotherapy • Threshold absorbed doses to the tumour <100 and ≥ 100 Gy (by local assessment)

549

550 **Supplemental Material 1: PROACTIF Registry Group Principal Investigators**

551

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585

586

589 **Supplemental Material 2: Planned Dosimetry Outcome Measures**

590 Evaluation of treatment targeting and dosimetry outcomes are defined as follows:

- 591 1) Concordance between location of tumor(s) at baseline (CT or MRI) and locations of lesions targeted by
592 ^{99m}Tc -MAA using ^{99m}Tc -MAA SPECT or SPECT/CT.
- 593 2) Concordance between location of tumor(s) at baseline (CT or MRI) and location of lesions targeted by Y-
594 90 using PET/CT, Y-90 PET/CT or PET/MRI, or Y-90 SPECT/CT.
- 595 3) Concordance between location of tumor(s) based on ^{99m}Tc -MAA (SPECT or SPECT/CT) and location of
596 tumor targeted by Y-90 using post-treatment Y-90 PET/CT, PET/MRI, or SPECT/CT.
- 597 4) Concordance between PVT at baseline and PVT targeted by ^{99m}Tc -MAA (SPECT or SPECT/CT) and Y-
598 90 (PET/CT, PET/MRI, or SPECT/CT).
- 599 5) Associations between pre-treatment tumor and normal tissue liver-absorbed doses with qualitative tumor
600 response (CR, PR), OS, and safety, respectively.
- 601 6) Association between post treatment tumor and normal tissue liver-absorbed doses with qualitative tumor
602 response (CR, PR), OS, and safety, respectively.
- 603 7) Association between pre and post treatment tumor and normal tissue liver-absorbed doses determined with
604 qualitative tumor response (CR, PR), OS, and safety, respectively.
- 605 8) Pre-treatment and post treatment absorbed dose determined for total perfused tumor, index lesion,
606 perfused normal tissue and whole liver normal tissue.
- 607 9) Pre-treatment and post treatment Dose Volume Histogram (DVH): as determined for total perfused tumor,
608 index lesion, and whole normal liver tissue.

609

Supplemental Material 3: Planned Advanced Dosimetry Analyses

All regression analyses will be conducted with both pre-procedural dosimetry and post-treatment dosimetry data. Cox regression analyses will be performed to determine the impact of tumor-absorbed dose on OS for patients with HCC and iCC. For patients with mCRC, a similar Cox regression analysis will be performed to evaluate the impact of absorbed dose to perfused liver on OS. Logistic regression analysis of qualitative tumor/index lesion response will be performed to assess the impact of the tumor/index lesion absorbed doses. In mCRC patients, a similar logistic regression analysis will be conducted to assess the impact of the absorbed dose to tumor and perfused liver on response; it is expected that most of these patients will be treated using standard dosimetry. In patients with HCC and iCC, logistic regression analyses of SAEs will be performed to evaluate association with non-tumoral liver absorbed doses in patients with HCC and iCC; a parallel analysis will be conducted for patients with mCRC to evaluate the impact of absorbed dose to normal liver tissue on SAEs. The relationship between absorbed doses will be assessed separately for non-tumoral liver-absorbed doses and tumor-absorbed doses using Bland-Altman analysis. A similar analysis will be performed for patients with mCRC to determine the relationship between absorbed dose to perfused liver volume and absorbed dose to normal tissue liver. In patients with HCC and iCC, linear regression of absorbed dose from pre-procedural dosimetry and post-treatment dosimetry data will be performed and Pearson's correlation coefficient will be calculated. In patients with mCRC, a linear regression will also be performed for absorbed dose to perfused liver volume and absorbed dose to normal tissue.