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THERASPHERE™ Y-90 Glass Microspheres | PROACTIF STUDY

PROACTIF: A Prospective, Real-World, Y-90 Study with TheraSphere for the Treatment of Liver Malignancies: Interim Analysis of 873 Hepatocellular Carcinoma (HCC) Patients

HIGH OVERALL SURVIVAL IN INTERMEDIATE AND ADVANCED HCC PATIENTS IN PROACTIF, THE LARGEST, PROSPECTIVE, REAL-WORLD Y-90 STUDY OF PRIMARY LIVER CANCER IN 1,000+ PATIENTS*

PROACTIF Overview

STUDY OBJECTIVE AND ENDPOINTS

The study aims to gather data on effectiveness, patient quality of life (QoL), and safety with use of TheraSphere Y-90 glass microspheres in real-world clinical settings in France.

Primary Endpoints

Overall survival (OS) from time of TheraSphere treatment and QoL, as assessed using the functional assessment of Cancer Therapy – Hepatobiliary (FACT-Hep) questionnaire.

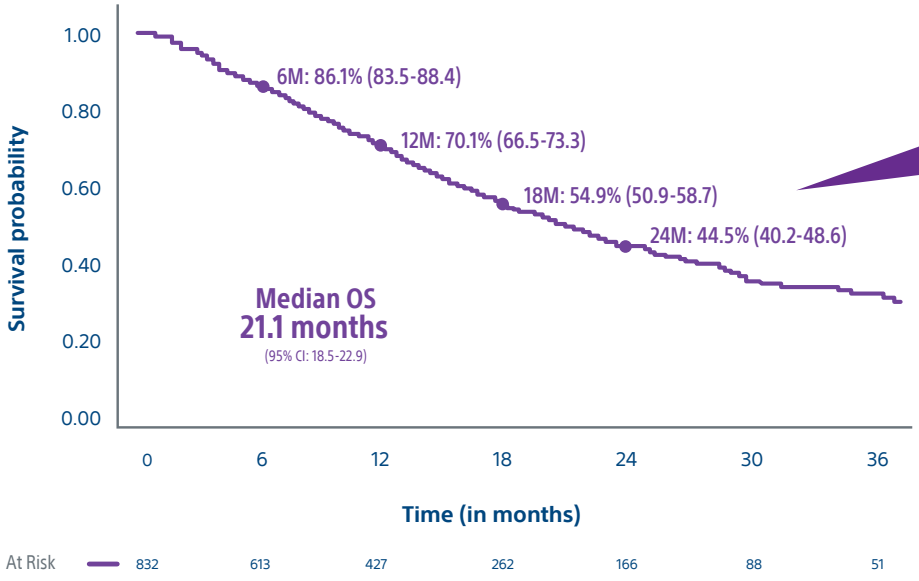
Key Secondary Endpoints

Grade ≥ 3 AEs, SAEs, tumor response, tumor marker response, subsequent therapy, and dosimetry evaluations.

First real-world, multi-center Y-90 study of primary liver cancer that builds on previously published TheraSphere landmark trials.

INTERIM HCC ANALYSIS - 873 PATIENTS ACROSS 32 SITES*

HIGH OVERALL SURVIVAL FOR INTERMEDIATE & ADVANCED STAGE HCC PATIENTS



MEDIAN OS
21.1 months
(95% CI: 18.5 – 22.9)

29.6 Months **BCLC B**
(95% CI: 22.3 – 39.8)

17.7 Months **BCLC C**
(95% CI: 15.7 – 20.6)

SUBGROUP ANALYSIS DEMONSTRATED PROLONGED SURVIVAL IN PATIENTS WHO RECEIVED SELECTIVE TREATMENT, WERE ALBI GRADE 1, OR HAD UNILOBAR DISEASE*

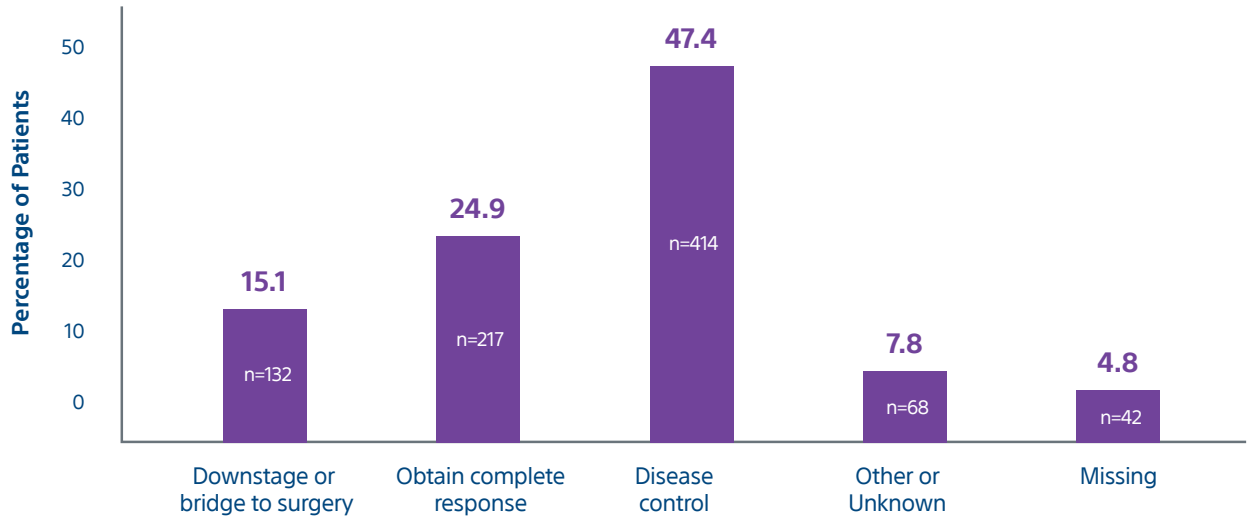
Subgroup	n	Median OS	95% CI
Administration			
Selective	**424**	**23.1 M**	**20.8-27.4**
Non-selective	**371**	**17.8 M**	**15.5-21.7**
ALBI Grade			
1	327	**29.4 M**	24.8-36.3
2 or 3	377	**17.0 M**	14.8-20.6
Disease extent			
Unilobar	650	**21.7 M**	19.7-24.8
Bilobar	157	**16.0 M**	13.7-18.3

DATA FROM 30+ SITES USED CONTEMPORARY TECHNIQUES AND DOSING*

70% MULTI-COMPARTMENT DOSIMETRY

49% SELECTIVE ADMINISTRATION

REAL-WORLD TREATMENT SCENARIOS SPAN CURATIVE TO PALLIATIVE INTENT



MAJORITY OF PATIENTS WERE INTERMEDIATE / ADVANCED STAGE WITH INDEX LESIONS > 5CM*

PATIENT DEMOGRAPHICS & DISEASE CHARACTERISTICS

Variable	n(%)	Variable	n(%)	Variable	n(%)
Age, median (years)	**71**	**ECOG performance status**		**BCLC stage**	
≥ 18 to < 65	228 (26.1)	0	494 (56.6)	0/A	1 (0.1)/ 28 (3.2)
≥ 65 to < 75	339 (38.8)	1	278 (31.8)	B	299 (34.2)
≥ 75	264 (30.2)	2	12 (1.4)	C	491 (56.2)
Missing	42 (4.8)	≥3	4 (0.5)	D	1 (0.1)
Gender		Missing	85 (9.7)	Missing	53 (6.1)
Male	781 (89.5)	**Extrahepatic disease**		**Portal vein thrombosis**	
Female	92 (10.5)	Yes	35 (4.0)	Yes	337 (38.6)
Etiology (top 5)		No	788 (90.3)	% segmental/lobar/main	19.4/15.6/3.4
Alcohol	421 (48.2)	Not assessed/Missing	50 (5.7)	No	521 (59.7)
Metabolic	203 (23.3)	**ALBI grade**		Missing	15 (1.7)
Hepatitis B/C	58 (6.6)/157 (18.0)	1	327 (37.5)	**Total lesions**	
None	145 (16.6)	2-3	377 (43.2)	1	356 (40.8)
Unknown/Other	93 (10.7)	Missing	169 (19.4)	2-4	400 (45.8)
Comorbidities (top 5)		**Child-Pugh**		>5	94 (10.8)
Alcohol intake sequelae	482 (55.2)	A	688 (78.8)	Missing	23 (2.6)
Arterial Hypertension	463 (53.0)	B	57 (6.5)	**Index lesion diameter**	
Diabetes	379 (43.4)	C	1 (0.1)	Median size, cm	6.20 cm
Smoking	333 (38.1)	Missing	127 (14.5)	≤ 5 cm	299 (37.9)
Coronary Artery Disease	110 (12.6)			> 5 cm	490 (62.1)

CONCLUSION

Interim analysis of 873 HCC patients across 32 sites demonstrated high overall survival in intermediate and advanced HCC patients. Data builds on evidence from previously published landmark trials such as DOSISPHERE and TARGET.

	PROACTIF (n=873)	DOSISPHERE-01 (ITT)[1]		TARGET[2] (n=209)
		MCD (n=31)	SCD (n=29)	
Study Design	Prospective, Real-World Study	Prospective, Randomized Controlled Trial		Retrospective, Real-World Study
BCLC A/B/C/D (%)	3.2/34.2/56.2/0.1	0/13/87/0	0/10/90/0	12.9/32.5/54.5/NAP
ECOG 0/1/≥2 (%)	56.6/31.8/1.8	58/24/0	0/48/52	64.6/32.1/3.4
CP A/B	78.8/6.5	A5: 81 A6 or B7: 19	A5: 79 A6 or B7: 21	89.5/10.5
PVT: none (%) seg/lobar/main (%)	59.7 19.4/15.6/3.4	36 33/30 (lobar or main)	27 31/41 (lobar or main)	66 NAV
Unilobar/bilobar disease (%)	74.5/18	58/42	41/59	70.8/29.2
Median OS (months)(95% CI)	**21.1 (18.5-22.9)**	**26.6 (11.7-NR)** **5 yr follow-up**: 24.8 (11.0-36.5)[3]**	**10.7 (6.0-16.8)** **5 yr follow-up**: 10.7 (6.0-14.9)[3]**	**20.3 (16.7-26.4)**

Data in above table as of December 2023.

This study is sponsored by Boston Scientific. Final results are expected in 2025 and will include full patient population with additional information on quality of life, safety and dosimetry.

AE = Adverse event. SAE = Serious adverse event.

*Interim data presented at SIR 2024. Data collection as of 12/30/2023. Final results are expected in 2025. ** Based on mITT population.

1. Garin E, Tselikas L, Guiu B et al. Personalized versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol. 2021, 6: 17-29.

2. Lam, M., Garin, E., Maccauro, M. et al. A global evaluation of advanced dosimetry in transarterial radioembolization of hepatocellular carcinoma with Yttrium-90: the TARGET study. Eur J Nucl Med Mol Imaging (2022). https://doi.org/10.1007/s00259-022-05774-0.

3. Garin E, Tselikas L, Guiu B, et al. Long-Term Overall Survival After Selective Internal Radiation Therapy for Locally Advanced Hepatocellular Carcinomas: Updated Analysis of DOSISPHERE-01 Trial. J Nucl Med. 2024;65(2):264-269. Published 2024 Feb 1. doi:10.2967/jnumed.123.266211

Garin E, Bailly C, Letang A et al. Abstract No. 257 • Featured Abstract The PROACTIF French Registry Study of Y-90 Glass Microspheres for the Treatment of Liver Malignancies: Interim Analysis of 670 Hepatocellular Carcinoma (HCC) Patients. J Vasc Interv Radiol. 2024 Mar 35(3):S113 doi: https://doi.org/10.1016/j.jvir.2023.12.295 (updated dataset for oral presentation at SIR March 2024)

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TheraSphere™ Yttrium-90 Glass Microspheres

INDICATION FOR USE: TheraSphere is indicated for use as selective internal radiation therapy (SIRT) for local tumor control of solitary tumors (1-8 cm in diameter), in patients with unresectable hepatocellular carcinoma (HCC), Child- Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status. **CONTRAINDICATIONS:** TheraSphere is contraindicated in patients: whose Tc-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract that may not be corrected by angiographic techniques • who show shunting of blood to the lungs that could result in delivery of greater than 16.5 mCi (0.61 GBq) of Y-90 to the lungs. Radiation pneumonitis has been seen rarely in patients receiving doses to the lungs greater than 30 Gy in a single treatment. • in whom hepatic artery catheterization is contraindicated, such as patients with vascular abnormalities or bleeding diathesis • who have pulmonary insufficiency (conventionally defined by an arterial oxygen pressure (Pa_2O2) of < 60 mmHg, or oxygen saturation (Sa_2O2) of < 90%) or severe liver dysfunction, including hepatic encephalopathy, clinically evident ascites or treatment with diuretics for ascites • with portal vein thrombosis (PVT) Type 4 involvement and lack of Tc-99m MAA deposition on the PVT seen on the Tc-99m MAA imaging with >70% tumor replacement in the liver • with comorbidities or poor overall health (e.g., ECOG performance status rating > 2) which may make the patient a poor candidate for locoregional radiation treatment. • who are pregnant. **WARNINGS:** The following pre-treatment, high-risk factors (disease characteristics) have been associated with serious adverse events deemed possibly related to use of the device: infiltrative tumor type • tumor nodules too numerous to count • AST or ALT > 5 times ULN • bilirubin > 2 mg/dL • tumor volume > 50% combined with albumin < 3 g/dL. Keep the TheraSphere dose vial upright and stored in its lead pot before and during patient treatment, except as required for radiation measurement. Do not open the dose vial acrylic shield prior to patient treatment. Post-treatment, waste materials require caution to prevent contamination and beta shielding due to residual glass microspheres. **PRECAUTIONS:** GENERAL PRECAUTIONS: As in any intra-arterial procedure, aseptic technique should be practiced, and care should be taken to ensure minimum patient anesthesia exposure extraneous to therapeutic objective. • Consideration of patient comorbidities should be used when determining the type and volume of fluid to infuse via catheter to avoid electrolyte imbalance, fluid shift, and hyperglycemia. • It is important to avoid any aggressive arterial procedure that may lead to arterial spasm that impairs TheraSphere distribution into the perfused liver target volume which may lead to underdosing or non- target deposition of TheraSphere. PRECAUTION IN PATIENTS WITH IMPAIRED LIVER FUNCTION: No efficacy or safety data from the LEGACY study are available to support the use of the device in patients with Child-Pugh score B or C cirrhosis. PRECAUTION IN VULNERABLE PATIENTS: No effectiveness or safety data are available to support the use of the device in children or breast- feeding women. ENDOCRINE DISRUPTION, CARCINOGENICITY, MUTAGENICITY, TOXICITY TO REPRODUCTION: Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses. RADIATION SAFETY: Radioactive products should be used only by healthcare professionals who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides. • As in the use of any radioactive material, ensure minimum radiation exposure to the patient extraneous to the therapeutic objective, and to minimize radiation exposure to workers and others in contact with the patient. RELEASE AND POST-TREATMENT PRECAUTIONS: Post treatment patient care: use universal precautions for body fluid contact. Trace Y-90 may be detectible in blood and urine; handle with gloves and dispose as normal body fluids. The radiation field is expected to be less than 1 mrem/h (10 µSv/h) at 3 ft (1 m) from the patient's abdomen. Supplemental shielding and segregation of the patient are not required to maintain exposure to others below regulated limits. • Release instructions: The patient should follow good hygiene (e.g., proper hand washing). Caregivers, family, and others do not require restrictions on patient contact; however, they can minimize their radiation exposure by avoiding prolonged time (>12 hours per day) within 1 ft (0.3 m) of the patient's abdomen for the first week post therapy. Patients should be advised that radiation emitted from the patient may be detectible at security screening (e.g., international travel). • Special precautions post-administration: If the patient requires hospitalization, surgery, medical assessment or treatment regarding any part of their thorax or abdomen within first 2 weeks of treatment, the patient should advise the hospital and treating physician of the Y-90 TheraSphere implant. The physician should consult their radiation safety staff for handling and disposal of liver tissue. • Special liver tissue handling: Special liver tissue handling may be required for post-treatment surgery, explant, or transplant since the glass microspheres remain permanently implanted in the liver tissue. Disclosure of the treatment will be required if cremation is considered. **POTENTIAL ADVERSE EVENTS:** The use of this product leads to irradiation of both tumorous and normal liver tissue. As a result, patients with compromised liver function may be at greater risk of liver function impairment and hence could experience complications. Clinical side effects usually occur within the first 4 to 6 weeks after treatment. Based on clinical trial data, literature reviews and post market surveillance, adverse events potentially associated with treatment using Y-90 microspheres, including TheraSphere, may include the following: Allergic reaction • Altered liver function, acute or chronic • Anorexia • Anxiety • Ascites • Bile Duct injury • Bleeding/hemorrhage • Chills / rigors • Cholecystitis (inflammatory or infectious) • Colitis • Death • Dehydration • Diarrhea • Dizziness • Dyspnea • Edema (any location) • Electrolyte abnormalities • Elevated BUN/creatinine • Fall • Fatigue • Fever • Gastrointestinal bleeding / hemorrhage • Gastrointestinal ulcer or ulceration • Hepatic encephalopathy • Hepatorenal failure • Hiccups • Hypertension • Hypotension • Infection (any location) • Liver failure, acute or chronic • Lymphopenia • Malaise • Mood alteration • Muscle weakness • Nausea • Neutropenia • Pain (any location) • Pancreatitis • Platelet count abnormalities • Pleural effusion • Portal hypertension • Pre-existing chronic liver disease decompensation • Pulmonary edema • Pulmonary fibrosis • Radiation hepatitis • Radiation induced disease, acute • Radio Embolization Induced Liver Disease (REILD) • Sepsis • Supraventricular arrhythmia • Thrombosis (arterial or venous) • Tumor inflammation (including tumor edema) • Tumor-lysis syndrome • Vomiting • Weight loss. Complications related to the administration procedure itself may include: Allergic reaction: Arterial injury including vessel dissection • Aspiration pneumonia • Bruising/bleeding/hematoma at site • Constipation/abdominal distension • Fatigue • Flushing • Infection • Nausea • Nerve damage. **CAUTION:** Federal (USA) law restricts this device to sale by or on order of a physician. PI-992004-AA. **Note:** Dose to the liver does not exceed 150 Gy.

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