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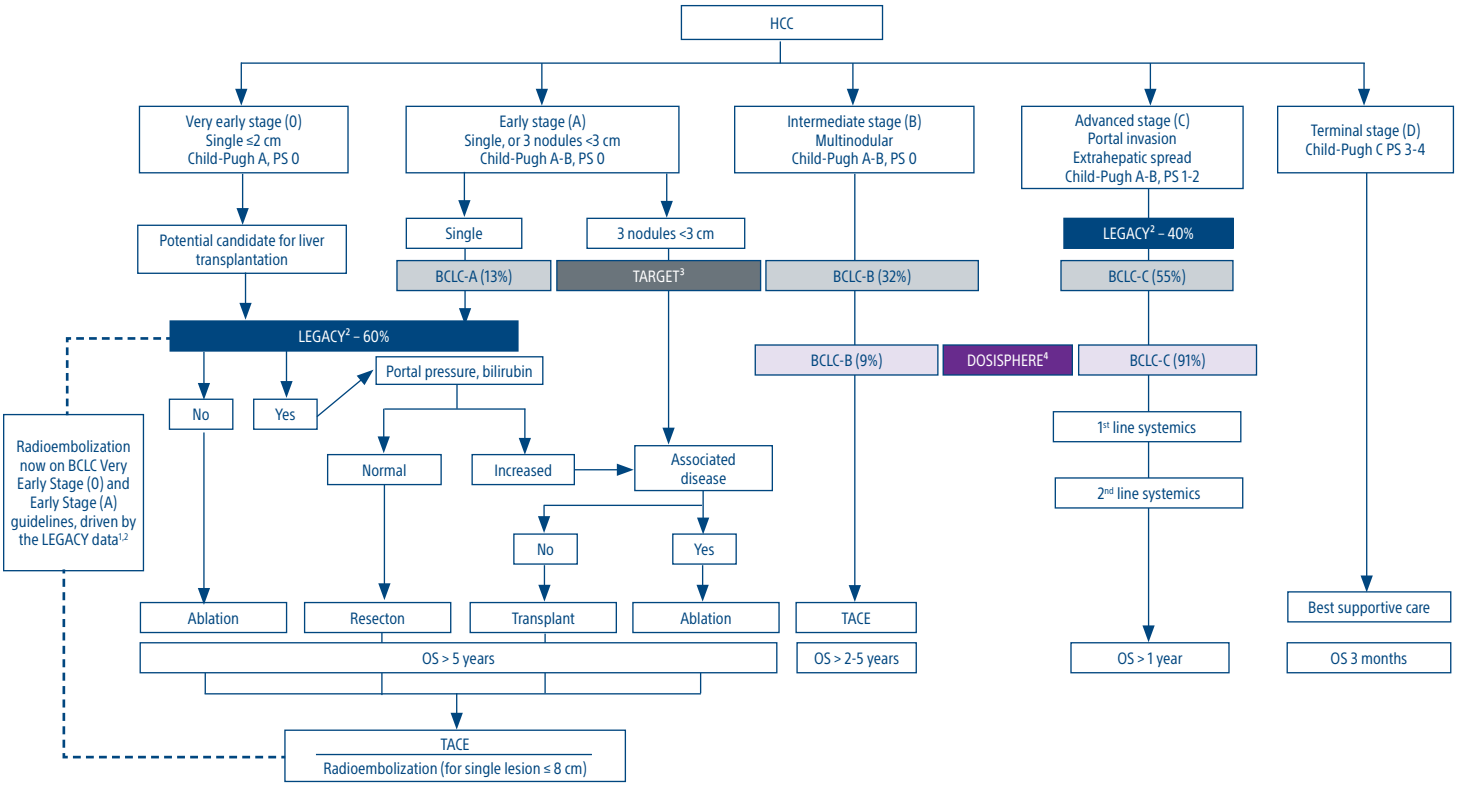
THERASPHERE™ Y-90 Glass Microspheres | Key Notable Trials

TheraSphere is a proven minimally invasive transarterial radiation therapy that delivers high-dose radiation directly to the tumor that yields strong local tumor control and prolongs survival without limiting hepatocellular carcinoma (HCC) patient's eligibility for future treatment.

STUDIED ACROSS MULTIPLE BCLC STAGES:

TheraSphere has been studied across a wide range of BCLC stages examining a variety of patients and disease characteristics. BCLC algorithm adapted to show patient population from key notable trials.



KEY TRIAL DESIGN AND BASELINE CHARACTERISTICS:

	LEGACY	DOSISPHERE-01	TARGET
Trial Design	Multi-center, U.S.	Multi-center, France	Multi-center, Global
	Retrospective	Prospective, randomized	Retrospective
	Single lesion	Single or multifocal† disease	Single or multifocal† disease
	N=169	N=60	N=209
Baseline Characteristics	BCLC: A, C	BCLC: B, C	BCLC: A,B,C
	BCLC C: **39.5%**	BCLC C: **87%***	BCLC C: **54.5%**
	PVT presence†: **0%**	PVT presence†: **65%***	PVT presence†: **33.0 %**
	Lesion size: Median **2.6 cm** (range: 0.9-8.1)	Index lesion: Mean±SD **10.6* cm** ±2.8	Target lesion**: ≥ 3 to < 5 cm: 19.6% ≥ 5 to < 8 cm: 34.4% **≥ 8 cm: 45.9%** **Median 7.3 cm** (range 3.1-17.4)
	Follow up: Median **29.9 M** (by reverse KM)	Follow up: Median **28.2 M**	Follow up: Median **13.1 M** (short term focus based on imaging availability)

*in multicompartmental study arm, ITT population
**target lesion with longest diameter using RECIST 1.1
†The safety and efficacy of TheraSphere in treatment of patients with PVT and/or multifocal disease has not been established.

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SAFE. TOLERABLE.

TheraSphere demonstrated a consistent safety profile with patients well-tolerating the treatment.

LEGACY		DOSISPHERE-01		TARGET	
5.6%	Low rates of device/procedure-related SAE's	**8.6%**	Low rate of patients experiencing ≥1 AE* (≥Grade 3) of personalized dosimetry approach (vs. 14.3% of standard dosimetry)	**4.8%**	of patients experienced ≥ Grade 3 hyperbilirubinemia in the absence of disease progression
3.1%	Low GI Disorders (abdominal pain, nausea, vomiting)				
0%	Patients experienced radiation-induced liver disease or failure				

*Liver AE related to Y-90

PREDICTABLE HIGH EFFICACY

TheraSphere showed strong local tumor control and a correlation of high absorbed radiation dose-to-survival outcomes.

	LEGACY	DOSISPHERE-01	TARGET
ORR in Target Lesion	**88%** best response (mRECIST)	**PDA: 71.4%** (EASL at 3 months)* **SDA: 35.7%** (EASL at 3 months)	**70.8%** best response (mRECIST)
Overall Survival	**83.5%** OS rate at 3 years (TheraSphere as primary treatment) **93.0%** OS rate at 3 years (TheraSphere followed by transplant or resection)	**PDA: 26.6 M**** **SDA: 10.7 M**	**20.3** months When TAD >300 Gy, OS was **36.7** months, 200 to <300 Gy, OS was **25.1** months, <200 to Gy, OS was **16.1** months

PDA: Personalized dosimetry arm | **SDA:** Standardized dosimetry arm | **TAD:** Tumor absorbed dose

*target lesion with longest diameter using RECIST 1.1
**in multicompartmental study arm, ITT population

TheraSphere, through its robust clinical trials data across a wide spectrum of HCC patients demonstrates:

- The role of minimally invasive transarterial radiation therapy that is well-tolerated by the patient.
- Ability to deliver high-dose radiation directly to the tumor yielding a strong local tumor control and prolongs survival.
- Maintains patient's eligibility for future treatment while providing strong efficacy.

1. Reig M et al., BCLC strategy for prognosis prediction and treatment recommendation Barcelona Clinic Liver Cancer (BCLC) staging system. The 2022 update Journal of Hepatology (2021), doi: https://doi.org/10.1016/j.jhep.2021.11.018.
2. Salem R, Johnson GE, Kim E, Riaz A, Bishay V, Boucher E, Fowers K, Lewandowski R, Padia SA. Yttrium-90 Radioembolization for theTreatment of Solitary, Unresectable Hepatocellular Carcinoma: The LEGACY Study. Hepatology. 2021 Mar 19. doi: 10.1002/hep.31819.
3. Lam, Marnix. A Global Study of Advanced Dosimetry in the Treatment of Hepatocellular Carcinoma with Yttrium-90 Glass Microspheres: Analyses from the TARGET Study. Presented at SIR. March 25, 2021.
4. Garin E, Tselikas L, Guiu B et al. Personalized versus standard dosimetry approach of selective internal radiation therapy inpatients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol. 2021, 6: 17-29

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,O2) of < 60 mmHg, or oxygen saturation (Sa,O2) 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 liver does not exceed 150 Gy.

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