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THERASPHERE™ Y-90 Glass Microspheres | DOSISPHERE-01 Trial

Level I randomized trial showed that unresectable HCC patients who receive a personalized TheraSphere dose using multicompartment dosimetry had a median OS of 26.6 months– a 16-month improvement compared to the control arm.

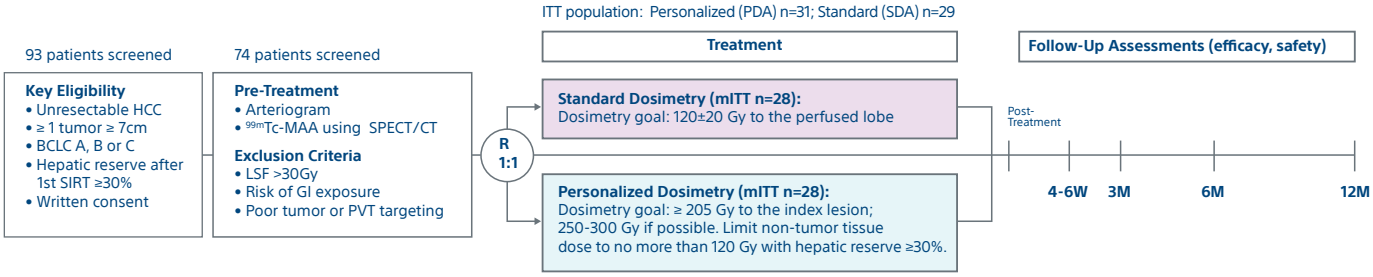
Garin E, Tselikas L, Guiu B et al. Personalized versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol. 2021, 6: 17-29

"Personalized dosimetry is safe and leads to a meaningful improvement in the objective response rate and overall survival of patients with locally intermediate/advanced hepatocellular carcinoma [...] when compared with standard dosimetry."

STUDY OBJECTIVE

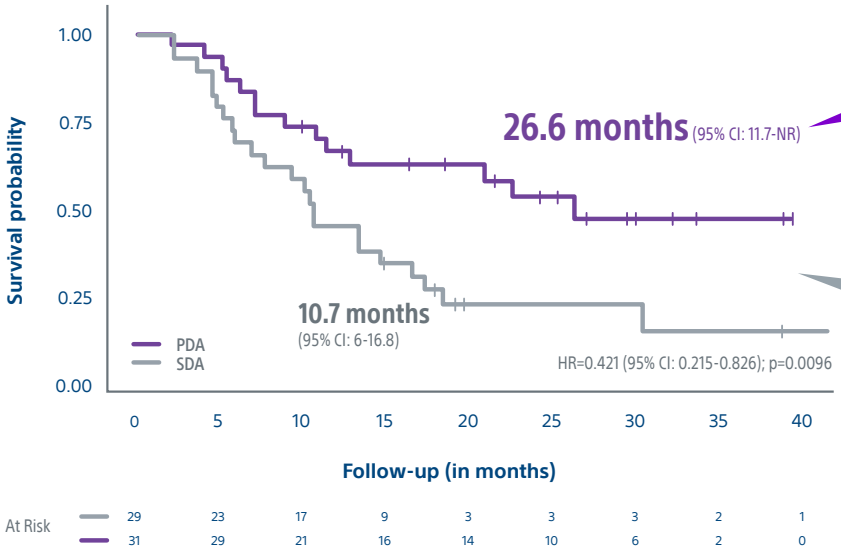
A **randomized, multicenter,** investigator sponsored phase II trial comparing the clinical outcomes of SIRT with TheraSphere in patients with intermediate/advanced HCC using two pre-treatment dosimetry determination methods: (1) Standard, single-compartment dosimetry (SDA); defined as a uniform distribution of absorbed dose within the perfused volume – both tumor and normal liver or (2) Personalized dosimetry (PDA); defined as multi-compartment Y-90 distribution of absorbed dose within the perfused volume that accounts for preferential blood flow into the tumor compared with normal parenchyma.

STUDY DESIGN



KEY RESULTS: PERSONALIZED DOSIMETRY IMPROVED SURVIVAL

MEDIAN OVERALL SURVIVAL (ITT POPULATION)



16 Month

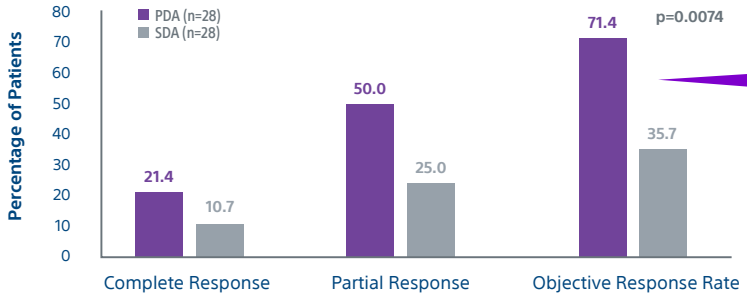
Survival Improvement
(personalized vs. standard dosimetry)

22.9 Month

Median Overall Survival for PVT patients in personalized arm vs. 9.5 months in standard arm

PERSONALIZED DOSIMETRY IMPROVED RESPONSE

INDEX LESION RESPONSE RATE AT 3 MONTHS USING EASL IN THE MITT POPULATION



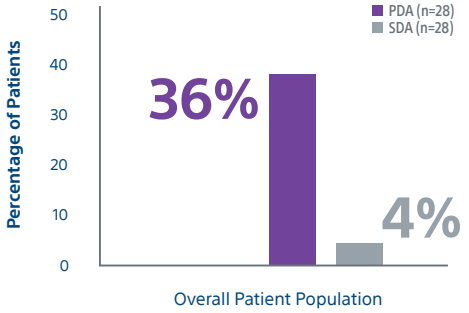
PRIMARY STUDY ENDPOINT

71.4%

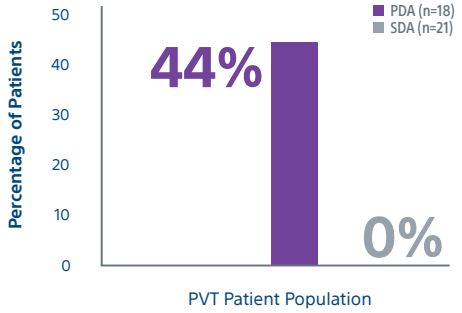
Objective Response Rate (personalized vs. 35.7% in standard dosimetry)

PERSONALIZED DOSIMETRY DOWNSTAGED MORE PATIENTS TO SURGERY

PATIENTS SUCCESSFULLY DOWNSTAGED TO SURGERY



36% of patients in the personalized arm were downstaged vs. 4% in the standardized arm



44% of PVT patients in the personalized arm were downstaged vs. 0% in the standardized arm

DOSISPHERE-01 EDITORIAL:

"The DOSISPHERE-01 Study challenges the evolving narrative that patients with advanced hepatocellular carcinoma should have systemic therapy at the expense of locoregional therapy. [...] Personalized dosimetry (ie, reaching specific threshold radiation doses) is a natural evolution of selective internal radiation therapy with ^{90}Y-labelled microspheres."[3]

– Robert J Lewandowski, MD, Riad Salem, MD, DOSISPHERE Editorial, Lancet Gastroenterology & Hepatology

1. Reasons for censoring: received another anti-cancer treatment before M3 evaluation (n=2), no evaluation at M3 evaluation (n=1) (10.7%)
2. Reasons for censoring: early deaths (before M3) (n=2), no evaluation at M3 (n=1), start another anti-cancer treatment before M3 evaluation (n=1) (14.3%)
3. Lewandowski, Robert J, Salem, Riad. Radioembolisation with personalised dosimetry: improving outcomes for patients with advanced hepatocellular carcinoma. Lancet Gastroenterol Hepatol 2020; Published Online: November 06, 2020 https://doi.org/10.1016/S2468-1253(20)30306-X

THERASPHERE™ Y-90 Glass Microspheres | DOSISPHERE-01 TRIAL

PATIENT DEMOGRAPHICS (mITT population)

Parameter	PDA (n=28)	SDA (n=28)
Male (%)	92.9	92.9
Child-Pugh Status (%)	CP A5: 78.6 CP A6/B7: 21.4	CP A5: 78.6 CP A6/B7: 21.4
BCLC (%)	BCLC B = 11 BCLC C = 89	BCLC B = 7 BCLC C = 93
Bilobar (%)	43	57
Mean Total Bilirubin (µM/L±SD)	14.0±6.4	14.3±6.4
PVT present (%)	64.3	75.0
PVT Location (%)	Segmental 29.6 Main/Lobar 30/33	Segmental 32.1 Main/Lobar 32/43
Index lesion (mean, cm)	10.5±2.4	10.9±2.57

TREATMENT CHARACTERISTICS AND DOSIMETRY (mITT population)

Investigator Assessments	PDA (n=28)	SDA (n=28)	*P* value
Number of Y-90 glass microspheres treatment	One treatment, n=26 Two treatments, n=2	One treatment, n=23 Two treatments, n=5	ns (*not significant*)
Activity administered GBq (mean, min-max)	3.6 (2.4-4.8)	2.6 (2.2-3.0)	0.0049
AD* to perfused liver (Gy) Mean (±SD)	178.4±59.9	120.3±15.2	0.0001
% of patients with AD to perfused liver> 150 Gy	68	4	<0.0001
AD to index lesion (Gy) Mean (±SD)	331.1±131.5	221.3±139.4	0.0007
% of patients with AD to index lesion > 205 Gy	88	38	<0.0008
AD to perfused normal tissue (Gy) Mean (±SD)	92.8±30.1	64.5±36.6	0.007

*AD=absorbed dose

LIVER ADVERSE EVENTS (Grade ≥3) Related to Y-90*

	PDA (n=35)	SDA (n=21)
Patients with ≥ 1 AE	3 (8.6%)	3 (14.3%)
Death	1 (2.8%)	1 (4.7%)
Liver AEs	4 (11.4%)	5 (23.8%)
Ascites	1	1
Encephalopathy	0	0
GI hemorrhage	0	2
Bilirubin increase/jaundice	1	2
Hepatic failure	2	0

*patients allocated to either PDA or SDA based on treatment received (dose received) versus allocation by randomization

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 the liver does not exceed 150 Gy.

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Peripheral Interventions
300 Boston Scientific Way
Marlborough, MA 01752-1234
www.bostonscientific.com

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