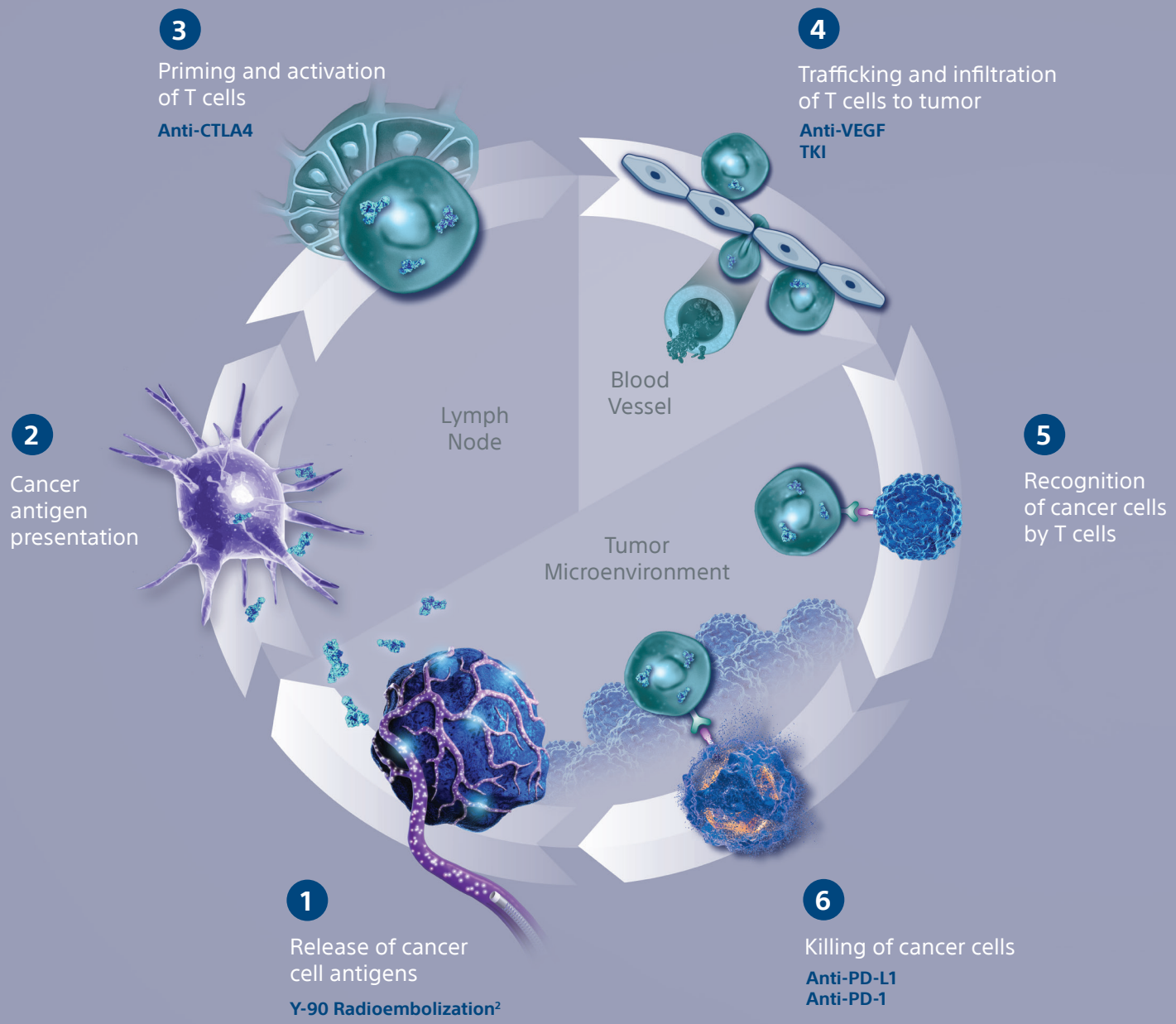
THERASPHERE™
Y-90 Glass Microspheres

Boston Scientific
Advancing science for life™

Y-90 & SYSTEMIC AGENTS | THE SCIENTIFIC PREMISE



Immunotherapy has revolutionized the management of cancer, including the treatment of hepatocellular carcinoma (HCC), improving clinical outcomes including disease control and overall survival[1,2]

Radiation therapy can stimulate the immune system through DNA damage, releasing tumor antigens to create a pro-inflammatory response at both the systemic level and local tumor microenvironment.[3] Immunotherapy agents work through activation of the immune system and rely on activation of immune T cells to destroy tumor cells.[4] Local therapies that help stimulate the immune system and improve tumor microenvironment (TMA) immunogenicity have potential to enhance the effectiveness of systemic immunotherapy agents.[5,6]

Radioembolization using glass Y-90 demonstrated sustained immune activation at the local and systemic immune level in a subset of patients characterized by an increase of systemic and local T cells.[2] Recent publications have highlighted the importance of further understanding TARE, and its ability to significantly enhance intra-tumor infiltrates in HCC, and the utilization in combination with immunotherapy.[6,7]

In a recent analysis of 1,664 eligible patients with advanced-stage HCC in the National Cancer Database, the combination of TARE and immunotherapy was associated with improved survival compared with immunotherapy alone. The findings in combination with the findings below underly the importance of large clinical trials evaluating combination therapy in these patients.[8]

Early Clinical (Abstracts) Studies Patient/Disease Baseline Characteristics[9,10]

Study	Therapy Protocol/Sequence	# of Patients	BCLC Stage (%)	Child-Pugh (%)	PVT/MVI (%)
A Pilot Study of Pembrolizumab in Combination with Y-90 Radioembolization in Patients with Poor Prognosis Hepatocellular Carcinoma (Hoosier Study, University of North Carolina)	Pembro every 3 weeks starting 7-10 days before initial Y-90 treatment P-> 1 week = Y-90 -> every 3 weeks = Pembro	29 Enrolled 27 Evaluable	Key eligibility: Locally advanced HCC with poor prognosis: PVT, multifocal, diffuse disease. C (100)	A (96) B7 (4)	Not reported**
Radioembolization with Y-90 Glass Microspheres in Combination with Durvalumab in Locally Advanced Unresectable Hepatocellular Carcinoma	Y-90 treatment followed by Durva 1500mg IV every 4 weeks	24 Enrolled 28 Evaluable	B (33.3) C (66.7)	A5 (87.5) A6 (12.5)	62.5*

*macrovascular invasion **criteria included PVT

Early Clinical Survival Evidence[9,10]

Study	Therapy Protocol/Sequence	mOS (months)	mPFS (months)	mTTP (months)
A Pilot Study of Pembrolizumab in Combination with Y-90 Radioembolization in Patients with Poor Prognosis Hepatocellular Carcinoma (Hoosier Study, University of North Carolina)	Pembro every 3 weeks starting 7-10 days before initial Y-90 treatment	27.3	9.95	9.95
Radioembolization with Y-90 Glass Microspheres in Combination with Durvalumab in Locally Advanced Unresectable Hepatocellular Carcinoma	Y-90 treatment followed by Durva 1500mg IV every 4 weeks	Not reached	6.9	15.2

Early Clinical Tumor Control Evidence[8,9]

Study	Therapy Protocol/ Sequence	Objective Response Rate (%)	Disease Control Rate (%)	CR (%)	PR (%)	SD (%)
A Pilot Study of Pembrolizumab in Combination with Y-90 Radioembolization in Patients with Poor Prognosis Hepatocellular Carcinoma (Hoosier Study, University of North Carolina)	Pembro every 3 weeks starting 7-10 days before initial Y-90 treatment	37.5 (mRECIST)	62.5	16.7	20.8	25
Radioembolization with Y-90 Glass Microspheres in Combination with Durvalumab in Locally Advanced Unresectable Hepatocellular Carcinoma	Y-90 treatment followed by Durva 1500mg IV every 4 weeks	83.3 (mRECIST)	91.7	29.2	54.2	8.3

Objective Response Rate = Complete Response + Partial Response

Disease Control Rate = Complete Response + Partial Response + Stable Disease

Early Clinical Safety Evidence[9,10]

Study	Therapy Protocol/ Sequence	TRAE (%)	Most Common (%)	Additional Comments
A Pilot Study of Pembrolizumab in Combination with Y-90 Radioembolization in Patients with Poor Prognosis Hepatocellular Carcinoma (Hoosier Study, University of North Carolina)	Pembro every 3 weeks starting 7-10 days before initial Y-90 treatment	48.1 (Grade 3/4)	Decreased lymphocytes (19), Elevated bilirubin (11), Elevated liver function tests (7)	4% (1 patient) experienced grade 5 hepatic failure and deemed related to Y-90
Radioembolization with Y-90 Glass Microspheres in Combination with Durvalumab in Locally Advanced Unresectable Hepatocellular Carcinoma	Y-90 treatment followed by Durva 1500mg IV every 4 weeks	47.8 (any Grade)	Hyperkalemia (8.7), Neutropenia (8.7), Fever (4.3), Chills (4.3), Palmer-plantar erythrodysesthesia syndrome (4.3), Urticaria (8.7), Nausea (4.3), Pneumonitis (4.3), Rash (4.3)	None experienced any treatment-related serious adverse events.

Liver Function Trends in Intermediate Stage (BCLC B) Patients Undergoing TARE

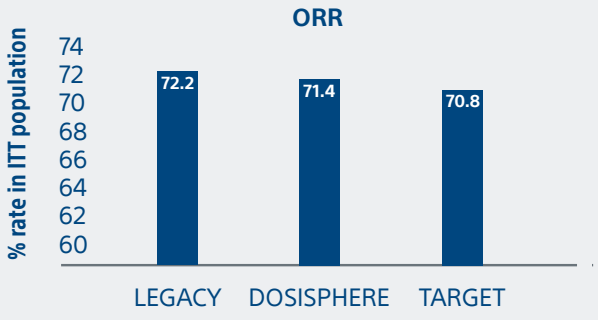
In a recent study, patients with intermediate stage disease and CP-A status treated with TheraSphere did not experience rapid hepatic decompensation precluding them from receiving benefits of systemic therapy.[11] The LEGACY data also reported 0% of patients experienced radiation induced liver disease or failure.[12]

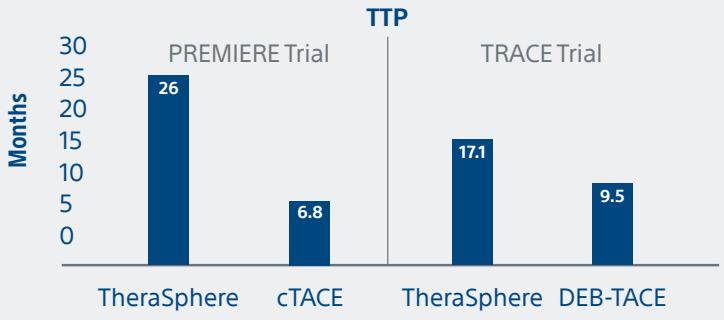
Those that converted to CP-B or -C after TARE were able to maintain adequate hepatic function for a measurable amount of time to allow for initiation of systemic therapies.[11]

Considerations of TheraSphere™ Y-90 Glass Microspheres

Added to BCLC and NCCN Guidelines as a recommended treatment option for hepatocellular carcinoma. BCLC included TARE as a treatment option given the results of the LEGACY trial.[13] NCCN Guidelines recommend a dose of >400 Gy to 25% of the liver or less in patients with Child-Pugh A liver function.

Targeting the tumor with minimal impact to the surrounding healthy liver, safely delivering high-dose radiation directly to the tumor yielding strong local tumor control.





TheraSphere patients have been shown to experience improved tolerability associated with QoL benefits and shorter hospital stays compared to TACE.[15-17] **Furthermore, TheraSphere, in one study was shown to be well-tolerated with minimal side-effects, demonstrating long-term preservation of health-related quality of life (HRQoL).[18]**

Boston Scientific's commitment to further study of Y-90 and Systemic Agents

ROWAN STUDY

The ROWAN Study

Immunotherapy using the single Tremelimumab regular interval Durvalumab (STRIDE) regimen has demonstrated superior overall survival to sorafenib in advanced HCC.[19] Recent work showed that TARE upregulates both the innate and adaptive immune systems. The possibility for TARE and STRIDE to have additive or synergistic effects when combined is of current scientific and clinical interest. The objective of the Phase II ROWAN Study is to assess the objective response rate and durability of local tumor control with TARE followed by STRIDE in HCC patients ineligible for surgery or thermal ablation.

Collaboration to advance clinical research

With **$30+M invested** globally, Boston Scientific is actively supporting clinically rigorous studies that assess safety and efficacy with TheraSphere and combination systemic therapies.

SCREENING

↓

ENROLLMENT
(n=100 evaluable patients)

1 to 14 days after enrollment

↓

DAY 1 - Administer Y-90 followed by post Y-90 dosimetry

7 to 21 days after Y-90 administration

↓

Duravalumab + Tremelimumab

Durvalumab Every 4 weeks, ±7 Days up to 18 months post Day 1

End of trial (18 months after last patient treated)

Radiological follow-up visits (every 8 weeks, ± 7 days, starting day 60) after Y-90 administration

HCC STAGE FOCUS

EARLY | INTERMEDIATE | ADVANCED

DRUG CLASSIFICATION TARGETS

PD-1 PD-L1 ± CTLA-4

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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,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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