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

Level 1 evidence showed that unresectable HCC patients who received a personalized TheraSphere dose using multi-compartment dosimetry and were downstaged to resection saw durable, long-term overall survival.

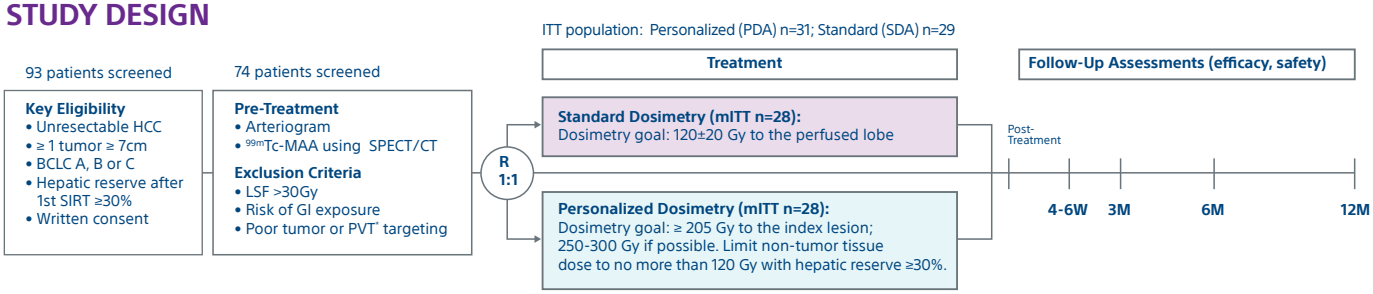
Garin E, Tselikas L, Guiu B et al. Personalized versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol. 2021, 6: 17-29.

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

STUDY OBJECTIVE

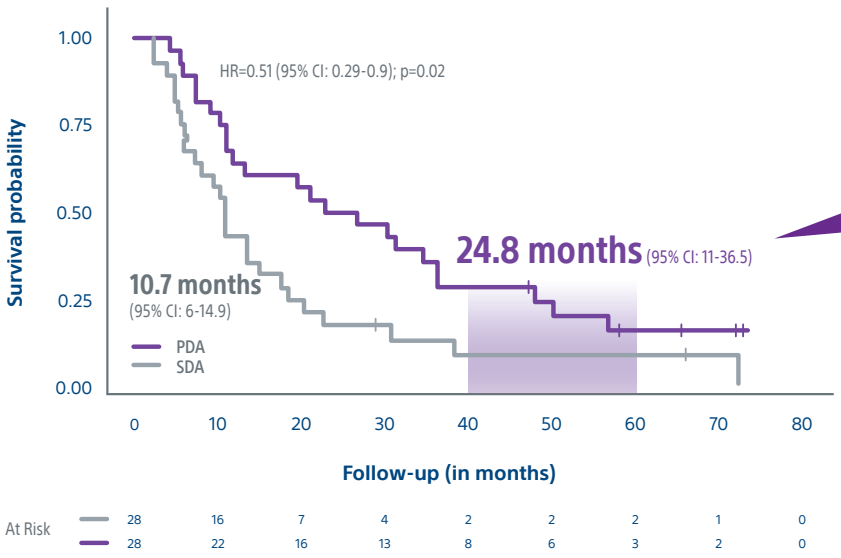
A **randomized, multicenter,** investigator sponsored phase II trial comparing the clinical outcomes of SIRT with TheraSphere in patients with intermediate/advanced HCC using two pre-treatment dosimetry determination methods: (1) Standard, single-compartment dosimetry (SDA); defined as a uniform distribution 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: AFTER ANALYSIS OF LONG-TERM 65.8 MONTH FOLLOW-UP, IMPROVEMENT IN MEDIAN OS WAS SUSTAINED IN THE PDA GROUP

MEDIAN OVERALL SURVIVAL (GLOBAL mITT POPULATION)



14.1 month

overall survival benefit for personlized vs. standard dosimetry

- 65% with PVT* involvement
- Mean tumor size 10.6 cm
- Personalized dosimetry effect generally consistent across subgroups

Results compare favorably with immunotherapy trials that reported median OS of 19.4 month (95% CI, 11–36.5 mo) with atezolizumab plus bevacizumab[1] and 16.4 month (95% CI, 14.1–19.5 mo) with durvalumab plus tremelimumab[2].**

1. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022;76:862–873.
2. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid. 2022;1:1–12.

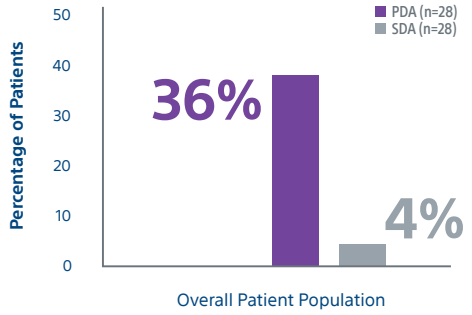
* TheraSphere not indicated for patients with PVT.

** IMbrave150 patient characteristics = unresectable HCC, Child-Pugh A, ECOG 0 or 1. Exclusion criteria was history of autoimmune disease, coinfection with hepatitis B & C viruses, and untreated or incompletely treated esophageal or gastric varices with bleeding or high risk of bleeding. STRIDE patient characteristics = unresectable HCC, BCLC B or C, Child-Pugh A, ECOG 0 or 1, & at least 1 measurable lesion per RECIST v1.1. Exclusion criteria was meaningful ascites, main PVT, or coinfection with hepatitis B & C viruses.

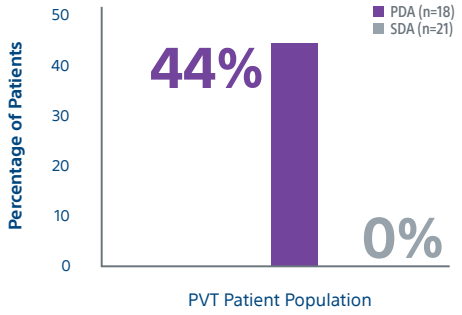
THERASPHERE™ Y-90 Glass Microspheres | DOSISPHERE-01 TRIAL

PERSONALIZED DOSIMETRY ALLOWED MORE PATIENTS TO BE DOWNSTAGED TO RESECTION, RESULTING IN DURABLE, LONG-TERM OVERALL SURVIVAL

PATIENTS SUCCESSFULLY DOWNSTAGED TO SURGERY

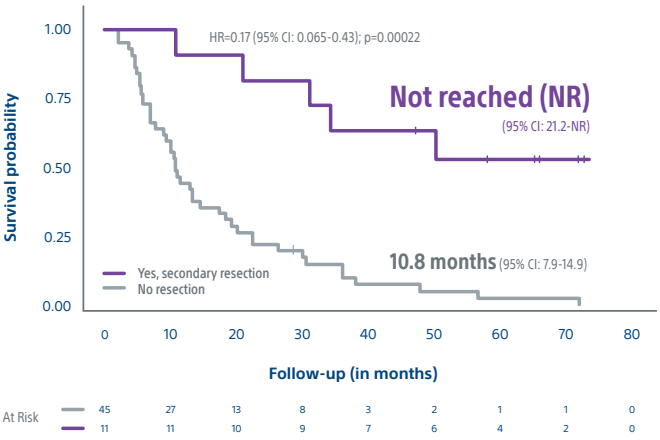


36% of patients in the personalized arm were downstaged vs. 4% in the standardized arm

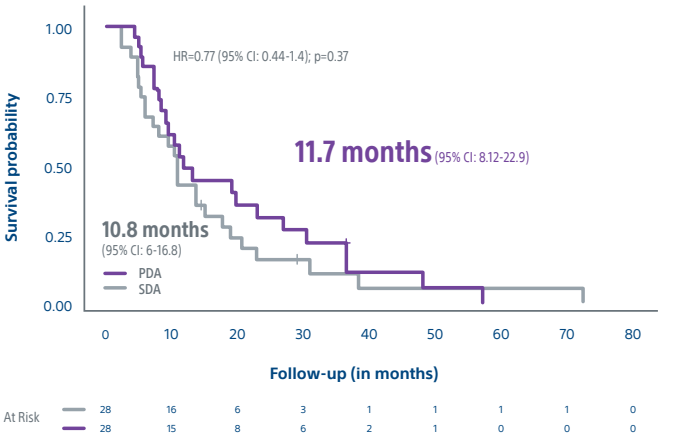


44% of PVT* patients in the personalized arm were downstaged vs. 0% in the standardized arm

MEDIAN OVERALL SURVIVAL (SECONDARY RESECTION STATUS)



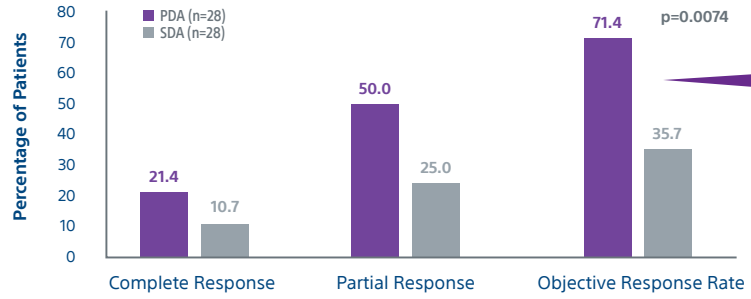
MEDIAN OVERALL SURVIVAL (GLOBAL mITT POPULATION CENSORED AT TIME OF SURGERY)



The prognostic impact of secondary surgery on long-term OS is highlighted by the loss of difference in median OS censored at the time of surgery between arms.

SIGNIFICANTLY IMPROVED RESPONSE RATE WITH PERSONALIZED DOSIMETRY

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)

* TheraSphere not indicated for patients with PVT.

OS rates decreased for patients with poor features (those randomly assigned to SDA, receiving a TD <205 Gy or a PLD <150 Gy, or not downstaged to resection). Only resected patients displayed an OS rate >50% at 5 years.

OS RATES FROM 2 TO 5 YEARS (mITT population)

Parameter	2 year	3 year	5 year
PDA	50.0 (34.5–72.4)	35.7 (21.7–58.7)	16.4 (6.8–38.9)
SDA	17.8 (8–39.5)	13.3 (5–35.5)	8.9 (2.5–31.5)
PVT* + (PDA)	44.4 (26.5–74.5)	33.3 (17.3–64.1)	5.6 (0.8–37.3)
PVT* + (SDA)	14.2 (5–40.7)	7.1 (1.2–40.6)	7.1 (1.2–40.6)
TD ≥ 205 Gy	48.5 (34.1–68.9)	35.7 (22.4–56.8)	18.3 (8.5–39.1)
TD < 205 Gy	13.3 (3.6–48.4)	13.3 (3.6–48.4)	6.7 (1–44.3)
PLD ≥ 150 Gy	48.3 (33.1–70.4)	37.1 (22.9–60)	20.9 (9.8–44.2)
PLD < 150 Gy	18.5 (8.3–40.9)	11.1 (3.8–32.3)	3.7 (0.5–25.3)
Resected	81.8 (61.9–100)	63.6 (40.7–99.5)	53.0 (29.9–94)
Not resected	22.2 (12.8–38.4)	15 (7.8–30.5)	2.5 (0.3–17.1)

Data in parenthesis are 95% CIs.

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

CONCLUSION

After a long-term follow-up period, a meaningful improvement in OS was sustained after personalized dosimetry. OS was dramatically improved for patients who were downstaged toward resection and then resected, including most PVT* patients. Because the 5 year survival rates for patients without resection remain low, randomized trials comparing SIRT with personalized dosimetry plus immunotherapy versus immunotherapy alone are now warranted in this specific patient population.

*TheraSphere not indicated for patients with PVT.

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ThereSphere™ Y-90 Glass Microspheres Indications, Safety, and Warnings

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