# HCC: A Year in Review

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# Disclosures

- Speaker & Consultant — Boston Scientific

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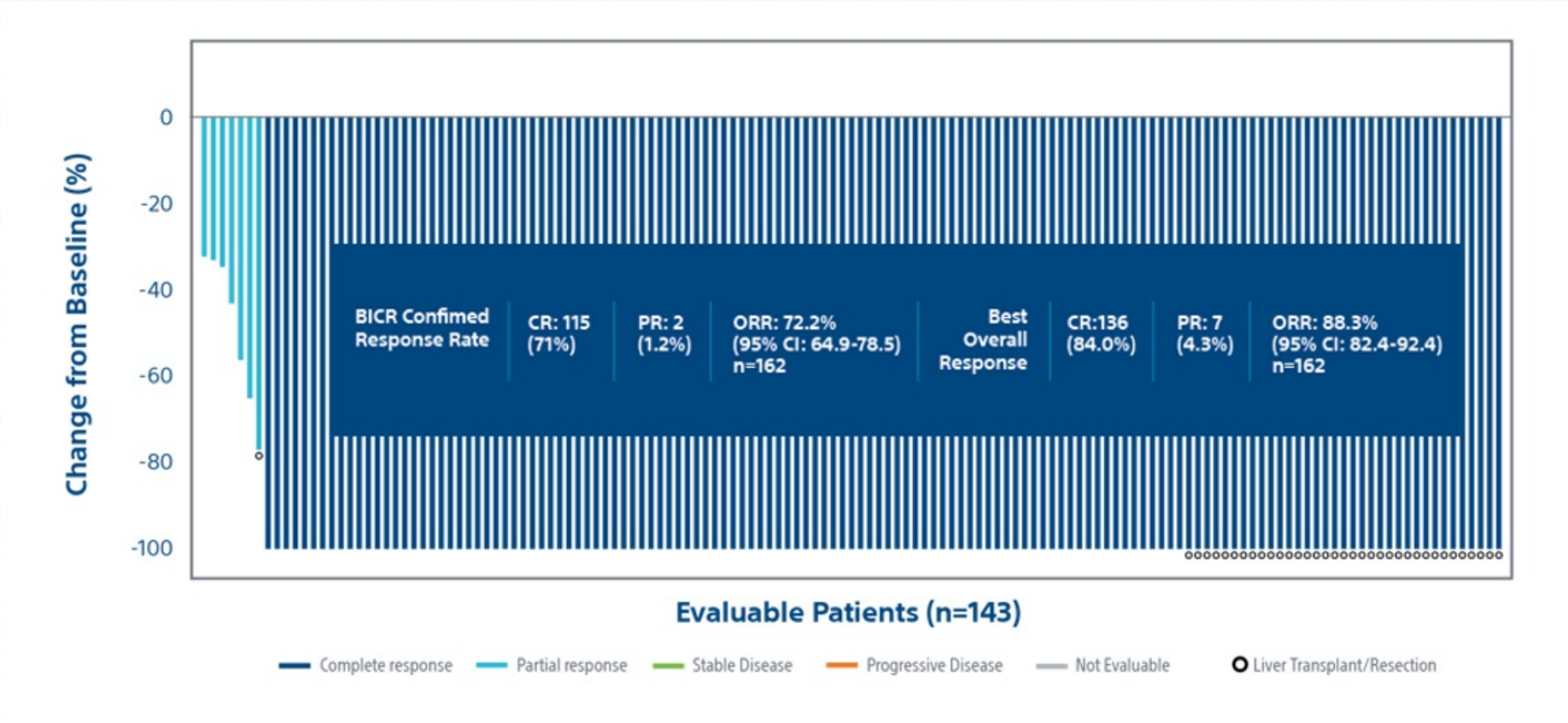
# LEGACY

- Multicenter, single-arm, retrospective study of consecutive patients treated from 2014-2017
- Inclusion criteria:
  - Solitary HCC </= 8 cm
    - Median tumor size 2.7
  - Child Pugh A
  - ECOG 0-1
- Exclusion criteria:
  - Prior LRT, LT or resection
  - Vascular invasion or extrahepatic disease
  - Clinically significant ascites or encephalopathy

# LEGACY

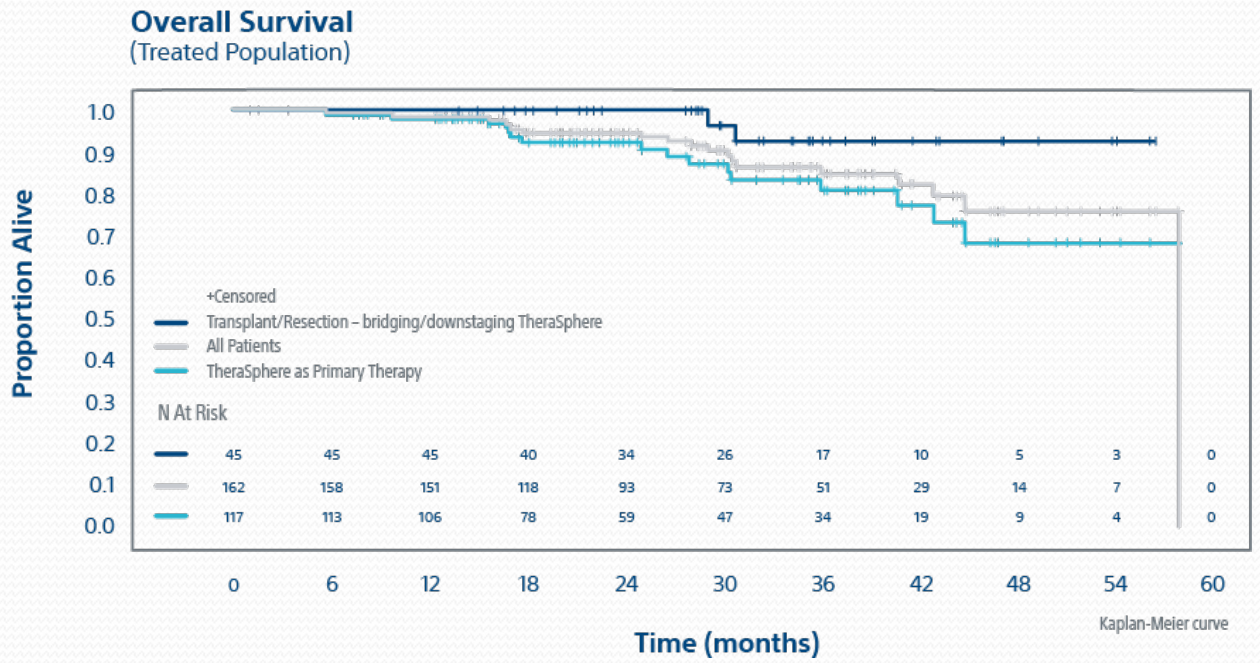
- Primary end points
  - Objective response rate (ORR) by localized mRECIST
  - Duration of response (DoR) by localized mRECIST
- Secondary endpoints
  - ORR/DoR by mRECIST/RECIST
  - Time to Progression (TTP)
  - Progression free survival (PFS)
  - Overall survival (OS)

# LEGACY




Salem et al. Hepatology 2021;

# LEGACY

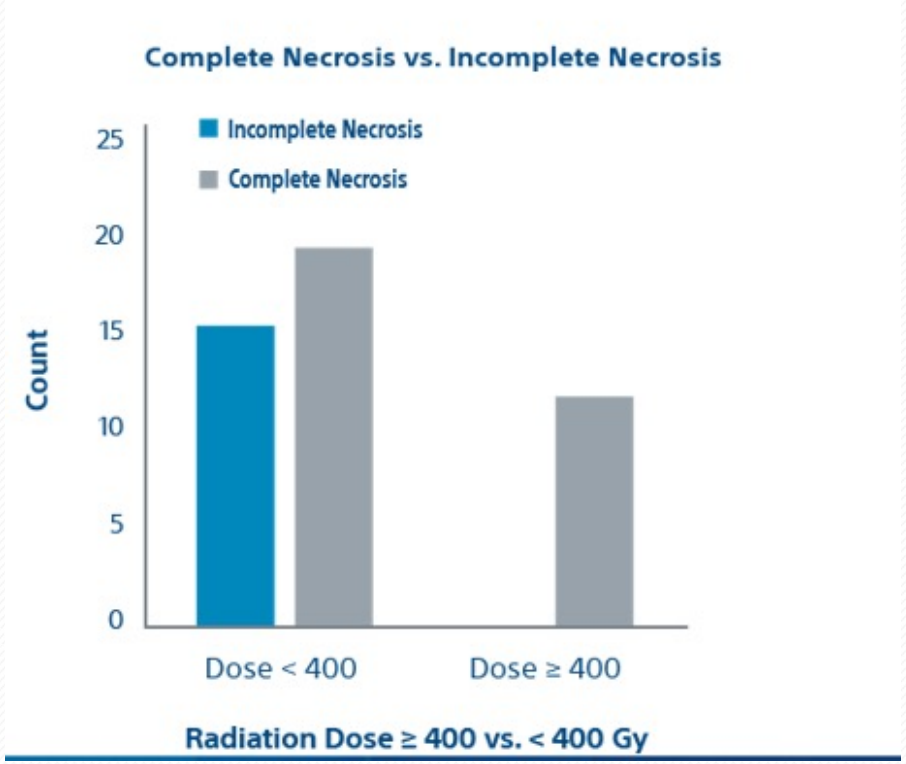



| | % Patients alive (95% CI) | |
|---|---|---|
| | 24 M | 36 M |
| Transplant/ resection (n=45) | 100 (100.0, 100.0) | 92.8 (74.2, 98.2) |
| TheraSphere as Primary Therapy (n=117) | 92.5 (84.7, 96.3) | 83.5 (72.2, 90.5) |
| All patients (n=162) | 94.8 (89.5, 97.5) | 86.6 (78.1, 92.0) |

Salem et al. Hepatology 2021; Online ahead of print

# Correlation of Y90-absorbed radiation dose to pathological necrosis in hepatocellular carcinoma: confirmatory multicenter analysis in 45 explants

Ahmed Gabr [1], Ahsun Riaz [1], Guy E Johnson [2], Edward Kim [3], Siddharth Padia [4], Robert J Lewandowski [1], Riad Salem [5]




Gabr et al. EJNMMI 2021; 48(2): 580-583

# Pathologic Response of Hepatocellular Carcinoma Treated with Yttrium-90 Glass Microsphere Radiation Segmentectomy Prior to Liver Transplantation: A Validation Study

Beau Toskich [1], Lucas L Vidal [2], Matthew T Olson [3], Jason T Lewis [3], Jordan D LeGout [4], David M Sella [4], S Ali Montazeri [2], Zlatko Devcic [2], Andrew R Lewis [2], Greg T Frey [2], Charles A Ritchie [2], Ricardo Paz-Fumagalli [2], Kristopher P Croome [5], Tushar C Patel [5]

- Single-institution retrospective analysis of HCC patients who received radiation segmentectomy prior to liver transplantation from November 2016 to May 2020

# Pathologic Response of Hepatocellular Carcinoma Treated with Yttrium-90 Glass Microsphere Radiation Segmentectomy Prior to Liver Transplantation: A Validation Study

Beau Toskich [1], Lucas L Vidal [2], Matthew T Olson [3], Jason T Lewis [3], Jordan D LeGout [4], David M Sella [4], S Ali Montazeri [2], Zlatko Devcic [2], Andrew R Lewis [2], Greg T Frey [2], Charles A Ritchie [2], Ricardo Paz-Fumagalli [2], Kristopher P Croome [5], Tushar C Patel [5]

- Objective response per mRECIST was 92% (CR: 76%; PR: 16%)
- 68% (n = 25) of tumors demonstrated ≥99% pathologic necrosis.
- Complete pathologic necrosis was present in 53% and 75% of tumors treated with >190 Gy (n = 18) and **>500** Gy (n = 8) using single compartment MIRD dosimetry

# DOSISPHERE

- Multicenter, randomized, prospective, open-label, phase two trial
- Arms:
  - Standard dosimetry: 120 Gy +/- 20 Gy to the perfused lobe (single compartment dosing)
  - Personalized dosimetry:
    - >205 Gy to the targeted index lesion using multicompartment dosimetry, and more than 250 Gy if possible
    - A dose of less than 120 Gy to normal liver

# DOSISPHERE

- Inclusion Criteria:
  - At least one measurable lesion >/= 7 cm
    - Personalized arm mean size 10.5 cm
    - Standardized arm mean size 10.9 cm
  - Hepatic reserve of >/= 30% after SIRT
  - Child-Pugh A or B
  - BCLC classification of A, B, OR C
- Exclusion Criteria:
  - Extrahepatic spread
  - >70% tumor involvement of the liver
    - Bilobar disease was permissible if there was limited disease in one lobe allowing for the 30% hepatic reserve
  - Previous TACE to the target lesion
  - Pulmonary shunting resulting in greater than 30 Gy dose to the lungs
  - GI shunting not correctable by embolization
  - Poor targeting of the index lesion on Tc99 MAA

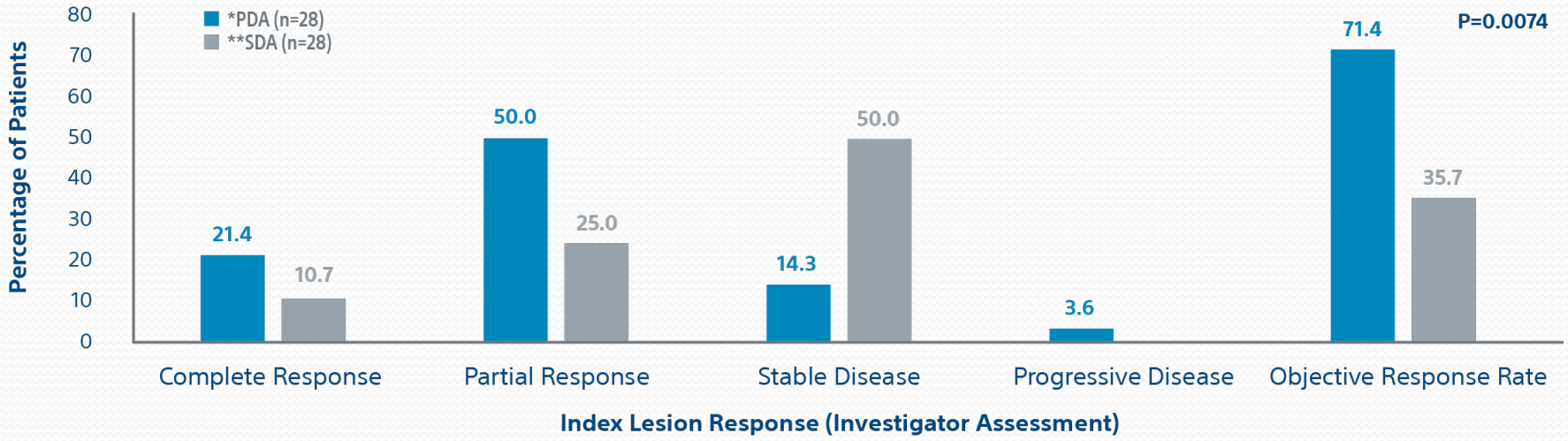
# DOSISPHERE

- Primary endpoint:
  - Objective response rate (ORR) of the largest index lesion in the modified ITT population at 3 months post Y-90 using EASL (investigator assessment)

- Secondary endpoints:
  - Dose response relationship
  - Safety
  - Progression free survival (PFS)
  - Overall survival (OS)

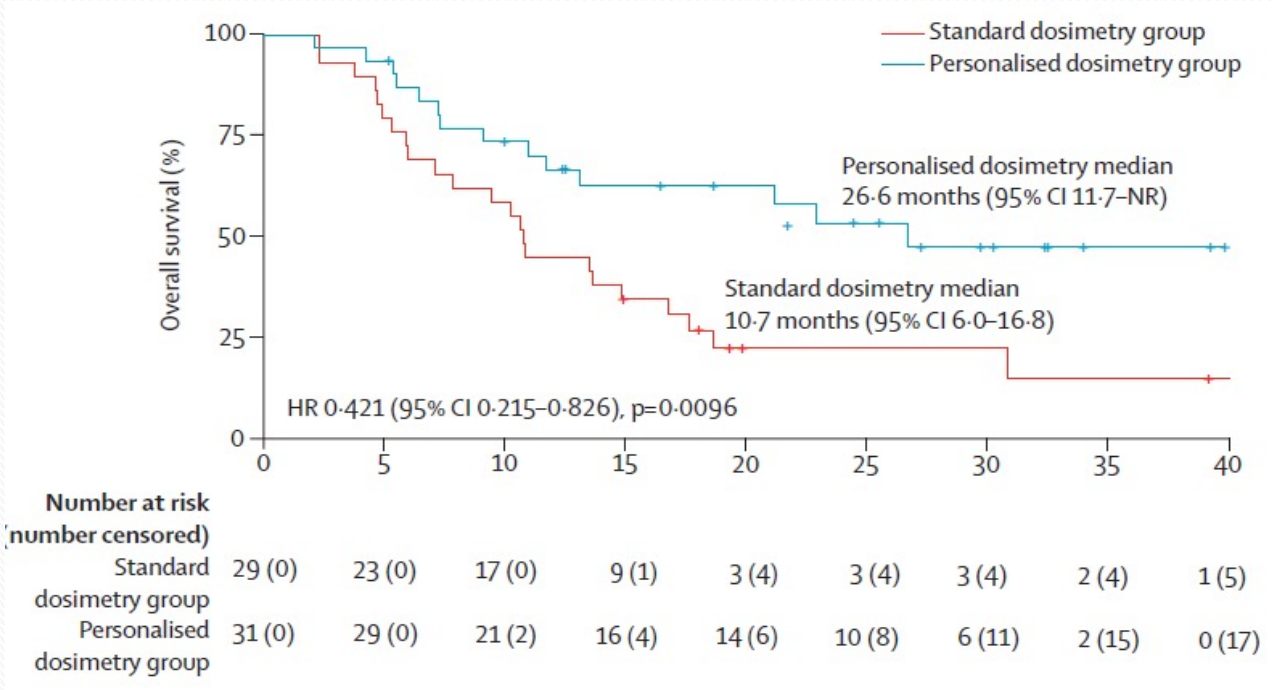
# DOSISPHERE

**PRIMARY END POINT:** INDEX LESION RESPONSE RATE AT 3 MONTHS USING EASL IN THE mITT POPULATION




Garin et al. Lancet Gastroenterol Hepatol 2020; 6(1):17-29

# DOSISPHERE




| Number at risk (number censored) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Standard dosimetry group | 29 (0) | 23 (0) | 17 (0) | 9 (1) | 3 (4) | 3 (4) | 3 (4) | 2 (4) | 1 (5) |
| Personalised dosimetry group | 31 (0) | 29 (0) | 21 (2) | 16 (4) | 14 (6) | 10 (8) | 6 (11) | 2 (15) | 0 (17) |

Garin et al. Lancet Gastroenterol Hepatol 2020; 6(1):17-29

# TARGET

- Retrospective, single-arm global study in 8 countries and 13 centers
  - Included 209 patients treated between January 2010 – December 2017
  - All sites used Simplicit$^{90}$Y™ software for co-registration, segmentation, and dosimetry
- Inclusion Criteria
  - Liver-dominant disease with or without portal vein thrombosis (PVT)
  - Single or multiple lesion but with ≤10 HCC tumors per lobe (at least one ≥3 cm)
  - Child-Pugh stage A or B7
  - BCLC stage A, B, or C
  - Unilobar or bilobar treatment

# TARGET

- Primary end points
  - Determine the normal tissue absorbed dose (NTAD), using pre-procedural $^{99m}$Tc-MAA SPECT or SPECT/CT imaging, to allow the calculation of the mean NTAD corresponding to a ≤15% probability of occurrence of hyperbilirubinemia*
- Secondary endpoints
  - Relationship between Overall Response Rate (ORR) and tumor absorbed dose (TAD)
  - Association between TAD and OS
  - Assess the relationship between tumor marker response (alpha fetoprotein, (AFP)) and TAD

# TARG

| Patient Characteristics | Treated Population (N=209) N (%) |
|---|---|
| **Median age (range), years** | 66.0 (27, 87) |
| **Gender, male** | 166 (79.4%) |
| **ECOG Status** | |
| 0 | 135 (64.6%) |
| 1 | 67 (32.1%) |
| 2 | 6 (2.9%) |
| 3 | 1 (0.5%) |
| **BCLC Status** | |
| A | 27 (12.9%) |
| B | 68 (32.5%) |
| C | 114 (54.5%) |
| **Child-Pugh Status** | |
| A (5-6) | 187 (89.5%) |
| B7 | 22 (10.5%) |
| **Unilobar or Bilobar Disease** | |
| Unilobar | 148 (70.8%) |
| Bilobar | 61 (29.2%) |

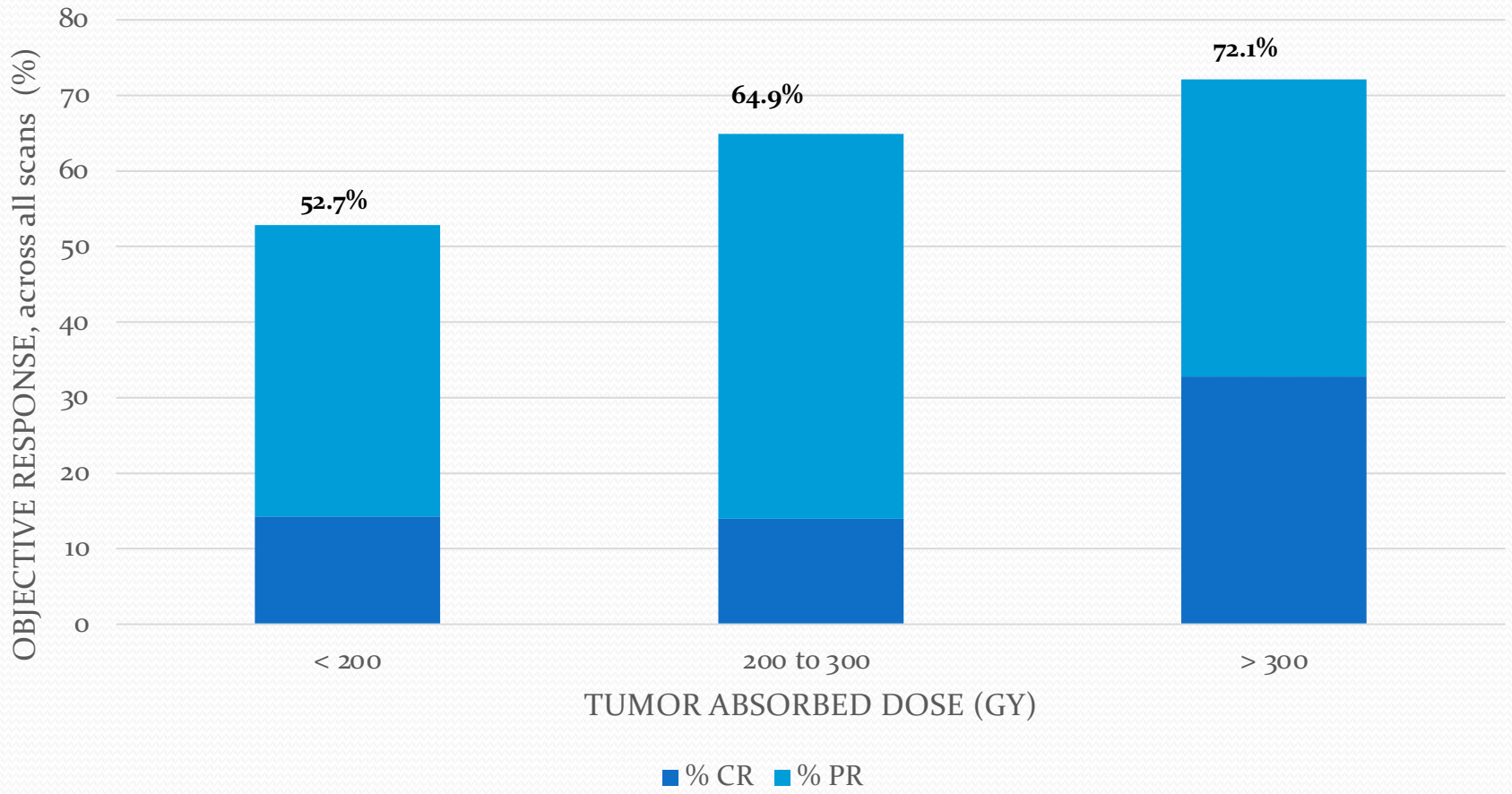
| Patient Characteristics | Treated Population (N=209) N (%) |
|---|---|
| **With PVT** | 69 (33.0%) |
| **Location of Target Lesion** | |
| Left Lobe | 30 (14.4%) |
| Right Lobe | 179 (85.6%) |
| **Target Lesion Longest Diameter (RECIST 1.1)** | |
| ≥3 to <5cm | 41 (19.6%) |
| ≥5 to <8cm | 72 (34.4%) |
| ≥8cm | 96 (45.9%) |
| **Total Number of Lesions (target and non-target)** | |
| 1 | 145 (69.4%) |
| 2 | 45 (21.5%) |
| 3 | 14 (6.7%) |
| 4-10 | 5 (2.4%) |

# TARGET

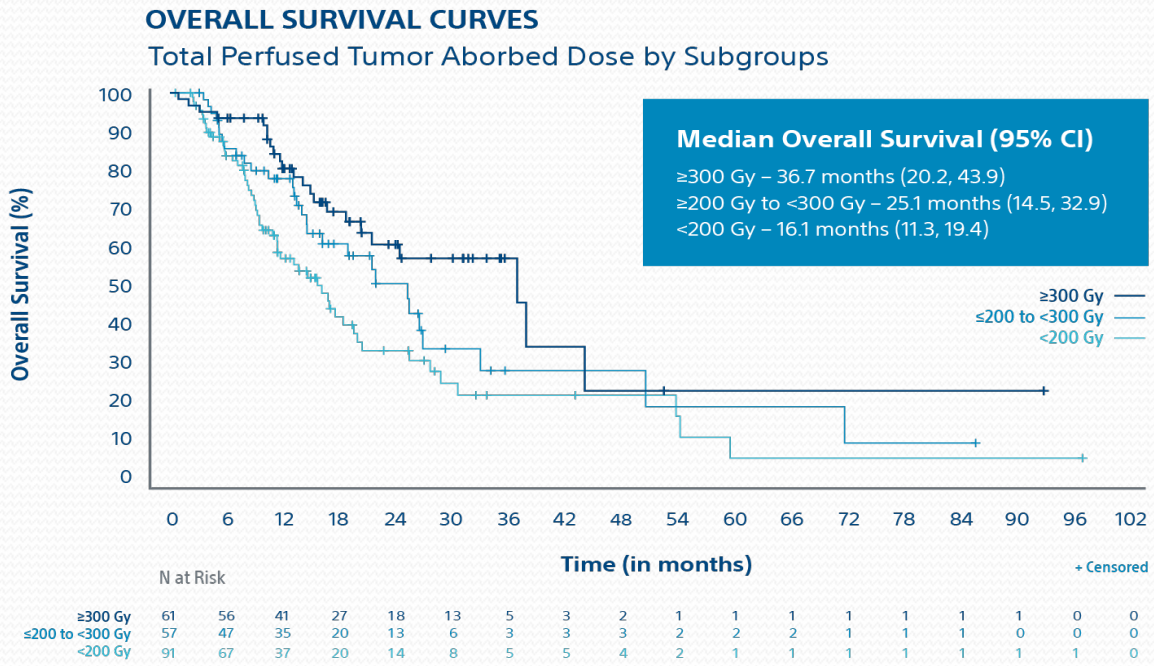
| | CTCAE Grade | | | | Total N=209 |
|---|---|---|---|---|---|
| | 1<br>n (%) | 2<br>n (%) | 3<br>n (%) | 4<br>n (%) | n (%) |
| **Patients with Observed Adverse Events** | 52 (24.9) | 36 (17.2) | 34 (16.3) | 9 (4.3) | 131 (62.7) |
| Ascites | 15 (7.2) | 13 (6.2) | 9 (4.3) | 1 (0.5) | 38 (18.2) |
| Fatigue | 22 (10.5) | 11 (5.3) | 1 (0.5) | 0 | 34 (16.3) |
| Abdominal pain | 18 (8.6) | 6 (2.9) | 2 (1.0) | 0 | 26 (12.4) |
| Elevated bilirubin[a] | 6 (2.9) | 15 (7.2) | 9 (4.3) | 0 | 29 (13.9) |
| Blood bilirubin increased | 6 (2.9) | 14 (6.7) | 5 (2.4) | 0 | 25 (12.0) |
| Hyperbilirubinemia | 0 | 0 (0) | 4 (1.9) | 0 | 4 (1.9) |
| Lymphocyte count decreased | 3 (1.4) | 6 (2.9) | 13 (6.2) | 3 (1.4) | 25 (12.0) |
| Asthenia | 14 (6.7) | 4 (1.9) | 1 (0.5) | 0 | 19 (9.1) |
| Decreased appetite | 10 (4.8) | 2 (1.0) | 0 | 1 (0.5) | 13 (6.2) |
| Nausea | 8 (3.8) | 3 (1.4) | 0 | 0 | 11 (5.3) |

**Only 4.8% of patients (10/209) experienced ≥ Grade 3 hyperbilirubinemia; threshold to reach primary endpoint was 15%**

# TARGET


80
70
60
50
40
30
20
10
0
OBJECTIVE RESPONSE, across all scans (%)
52.7%
64.9%
72.1%
< 200
200 to 300
> 300
TUMOR ABSORBED DOSE (GY)
% CR
% PR

# TARGET




**Increase in tumor absorbed dose independently associated with increased overall survival**

Overall Survival Hazard Ratio (corresponding to every 100 Gy change in tumor absorbed dose) = 0.826 (95% CI: 0.71, 0.95; p=0.009)



Lam M et al. Oral presentation at SIR, March 2021

# Recent studies

| | LEGACY | DOSISPHERE-01 | TARGET |
|---|---|---|---|
| **Summary** | Retrospective, multi-center study (US) to measure ORR and DoR | Prospective, multi-center randomized control trial (France) to examine ORR with personalized dosimetry | Retrospective, multi-center study (global) to establish correlation between TAD and outcomes |
| **Patients** | Early and Advanced HCC – CP A, ECOG 0/1, no PVT, solitary lesion | 90% Advanced HCC – 80% CP A, 10.6 cm mean lesion, 65% PVT* | BCLC A, B and C patients – 90% CP A, 7.3 cm median lesion, 33% PVT* |
| **Treatment** | Radiation Segmentectomy (93%) 410 Gy median dose to perfused volume | Personalized Arm: multi-compartment dosimetry targeting >/= 205 Gy to tumor | Unilobar or bilobar (radiation segmentectomy excluded)"; TAD and NTAD confirmed retrospectively using Simplicit$^{90}$Y |
| **Objective Response** | 88.3% best response mRECIST | Personalized Dosimetry: 71.4% Standard Dosimetry: 35.7% *EASL at 3 months* | 70.8% mRECIST |
| **Overall Survival** | 93% OS rate at 3 years (Y-90 followed by surgery)<br><br>83.5% OS rate at 3 years (Y-90 as primary treatment) | Personalized: 26.6 months Standard: 10.7 months | 20.3 months |

1. Salem R, Johnson GE, Kim E, Riaz A, Bishay V, Boucher E, Fowers K, Lewandowski R, Padia SA. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable Hepatocellular Carcinoma: The LEGACY Study. Hepatology. 2021 Mar 19. doi: 10.1002/hep.31819. 2. 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. 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.

# Liver Transplantation Following Yttrium-90 Radioembolization: 15-Year Experience in 207-Patient Cohort

Ahmed Gabr, Laura Kulik, Samdeep Mouli, Ahsun Riaz, Rehan Ali, Kush Desai, Ronald A. Mora, Daniel Ganger, Haripriya Maddur, Steven Flamm, Justin Boike ... See all authors

- Retrospective study looking at 207 patient who underwent liver transplantation following y90 analyzing for long-term outcomes including overall survival, recurrence-free survival, disease specific mortality and time-to-recurrence

Gabr A, Kulik L, Mouli S, Riaz A, Ali R, Desai K, Mora RA, Ganger D, Maddur H, Flamm S, Boike J, Moore C, Thornburg B, Alasadi A, Baker T, Borja-Cacho D, Katariya N, Ladner DP, Caicedo JC, Lewandowski RJ, Salem R. Liver Transplantation Following Yttrium-90 Radioembolization: 15-Year Experience in 207-Patient Cohort. Hepatology. 2021 Mar;73(3):998-1010. doi: 10.1002/hep.31318. Epub 2020 Nov 7. PMID: 32416631.

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- 3-year, 5-year, and 10-year OS rates were 84%, 77%, and 60%, respectively.
- Median RFS of 120 (95% confidence interval, 69-150) months.
- DSM at 3, 5, and 10 years was 6%, 11%, and 16%, respectively. There were no differences in OS/RFS for patients who were bridged or downstaged

Gabr A, Kulik L, Mouli S, Riaz A, Ali R, Desai K, Mora RA, Ganger D, Maddur H, Flamm S, Boike J, Moore C, Thornburg B, Alasadi A, Baker T, Borja-Cacho D, Katariya N, Ladner DP, Caicedo JC, Lewandowski RJ, Salem R. Liver Transplantation Following Yttrium-90 Radioembolization: 15-Year Experience in 207-Patient Cohort. Hepatology. 2021 Mar;73(3):998-1010. doi: 10.1002/hep.31318. Epub 2020 Nov 7. PMID: 32416631.

# DOORwaY90: ongoing

- Primary Endpoints
  - Overall Response Rate (ORR) by localized mRECIST criteria and best response through 9 months, in patients treated with SIR-Spheres Y-90 resin microspheres.
  - Duration of Response (DoR) from first time of response (complete response or partial response) until disease progression (PD) as defined by localized mRECIST criteria.

# DOORwaY90: Ongoing

- Secondary Endpoints
  - Grade ≥ 3 toxicity at 2 months and 6 months
  - Incidence of liver resection post-procedure follow-up: 1, 2, 4, 6, 9, 12, 24 months
  - Incidence of liver transplant post-procedure follow-up: 1, 2, 4, 6, 9, 12, 24 months
  - Quality of life metrics - Pre-procedure, 2, 4, 6, 9, and 12 months

# Questions?

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