A Global Evaluation of Advanced Dosimetry in Radioembolization of Hepatocellular Carcinoma: Analyses from the TARGET Study

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Study Objectives

- To evaluate the relationship between tumor and normal tissue absorbed dose (TAD and NTAD) with objective response (OR) and adverse events (AEs) in hepatocellular carcinoma (HCC) patients treated with yttrium-90 (90-Y) glass microspheres.
- To evaluate the reproducibility of TAD and NTAD assessments between investigators

Study Design

- Retrospective, single-arm study of 209 patients from 13 centers across 8 countries
- Key Inclusion Criteria:
  - Liver-dominant disease with or without portal vein thrombosis (PVT).
  - Unilobar or bilobar administration of 90-Y glass microspheres (TheraSphere™)
  - ≤10 HCC tumors per lobe (at least one ≥3 cm)
  - Child-Pugh stage A or B7
  - BCLC stage A, B, or C
  - No prior intra-arterial treatment
- Multicompartment pre-treatment dosimetry was retrospectively determined with Simplicit90Y™ software (Mirada Ltd.)
- Multicompartment dosimetry inter-observer reproducibility was evaluated by the reproducibility coefficient (RDC) for TAD and NTAD (on 8 reviewers at 8 centers for 20 patients)
  - RDC representing the maximum ratio of the dosimetric measurement between 2 reviewers was computed using a random effects model on log transformed data

Primary Endpoint

- Relationship between NTAD and the occurrence of ≥Grade 3 hyperbilirubinemia, in the absence of disease progression,.

Secondary Endpoint

- Relationship between objective response rate (ORR) by mRECIST and TAD
- Relationship between Overall Survival (OS) and TAD
- Relationship between tumor marker (alpha fetoprotein [AFP]) response and TAD
- Relationship between AEs and NTAD
- Inter-observer reproducibility of TAD and NTAD

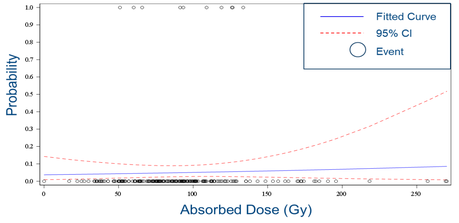
Table 1: Baseline Characteristics

Patient Characteristics	Treated Population (N=209) N (%)
Median age (range), years	66 (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%)
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%)

Note: "Target lesion" is the lesion with the greatest diameter

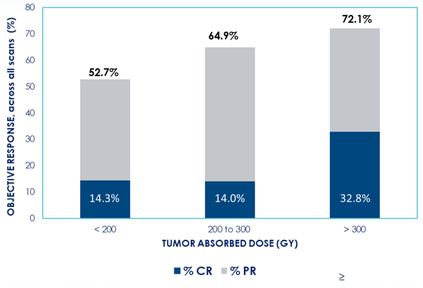
Results

Figure 1: Probability of ≥ Grade 3 Hyperbilirubinemia and Normal Tissue Absorbed Dose



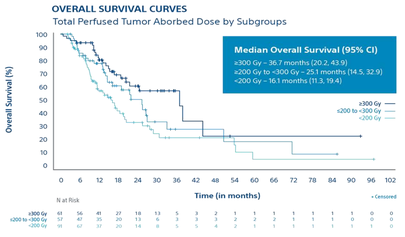
- Only 10 patients (4.8%) experienced ≥ Grade 3 hyperbilirubinemia
- There were too few patients to determine a relationship with NTAD (p=0.6 by logistic regression)

Figure 2: Objective Response Rate (mRECIST) and Total Perfused Tumor Absorbed Dose



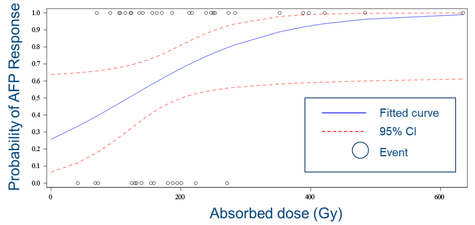
- ORR (mRECIST) was 61.7% over all lesions (129/209; 95% CI = 55.0%, 68.0%)
- ORR (mRECIST) was 70.8% for the target lesion (148/209; 95% Confidence Interval [CI] = 64.3%, 76.6%)
- Responders (n=129) had a significantly higher geometric mean TAD (225.5 Gy: 95% CI = 201.0 Gy, 253.0 Gy) compared with non-responders (n=80) (188.3 Gy: 95% CI = 164.6 Gy, 215.3 Gy; p=0.048 by 2-sample t-test)

Figure 3: Overall Survival



- Increase in TAD is associated with increased OS
- OS Hazard Ratio [HR] = 0.826 (95% CI= 0.71, 0.95; p=0.009 by Cox regression)
  - HR of 0.826 corresponds to 17.4% improvement in survival probability (on the log scale) for every 100 Gy increase in TAD

Figure 4: Alpha Fetoprotein (AFP) Response 90 Days Post-Treatment



- 38.0% (27/71) of patients with AFP ≥200 ng/mL at baseline had a response (a ≥50% decrease) at 90 days post-treatment
- Increase in TAD was associated with increased probability of AFP response at 90 days post-treatment (p=0.046 by logistic regression)

- The RDC for total perfused TAD was 1.84 (95% CI: 1.66, 2.56); for total perfused NTAD tissue was 1.46 (95% CI: 1.39, 2.25)

Discussion

- The low rate of ≥ Grade 3 hyperbilirubinemia denotes the safety of the treatment, in patients treated per instruction for use recommendation
- Higher TAD is associated with better overall survival
  - This is in line with recently published results
- Dose-efficacy relationship was confirmed (imaging and tumor-marker response)
  - Increased probability of tumor response and AFP response with higher TAD
- Pre-treatment dosimetry using ^{99m}TC-MAA as a surrogate is a clinically meaningful tool for dose determination and response expectations

Conclusions

- No relationship could be determined between NTAD and ≥ Grade 3 Hyperbilirubinemia. The rare occurrence of events confirms the safety profile of TheraSphere and opens room for optimization of TAD.
- The range of total perfused TAD values evaluated (14 Gy – 1130 Gy) supports the correlation between higher TAD and improved response and survival
- The advanced dosimetry methods demonstrated acceptable inter-observer reproducibility, indicating multicompartment dosimetry using Simplicit^{90}Y produced consistent results in a variety of clinical settings

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