The TARGET Study: A Global Investigation of Advanced Dosimetry for Transarterial Radioembolization of Hepatocellular Carcinoma with Yttrium-90 Glass Microspheres

#934P

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Study Objectives

Primary Objectives: To collect clinical data to evaluate relationships between tumor and normal absorbed dose (TAD and NTAD), adverse events (AEs), and objective response (OR) in hepatocellular carcinoma (HCC) patients treated with yttrium-90 (90-Y) glass microspheres.

Study Design

- Global, 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 Simplicit^{90}Y™ software (Mirada Ltd.)

Endpoints

- Primary Endpoint: Relationship between AEs of ≥Grade 3 hyperbilirubinemia, in the absence of disease progression, and NTAD
- Secondary Endpoints:
  - Relationship between objective response (ORR) by mRECIST and total perfused TAD
  - Where response is defined as complete or partial response (CR or PR)
  - Relationship between Overall Survival (OS) and TAD
  - Relationship between tumor marker (alpha fetoprotein [AFP]) response and TAD
  - Relationship between AEs and NTAD

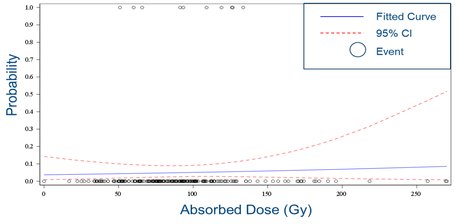
Results

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%)
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%)

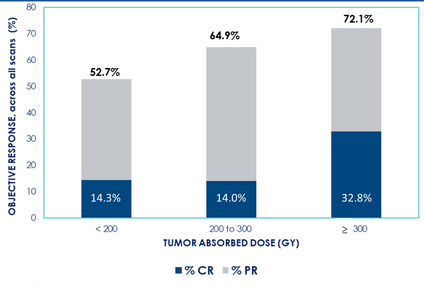
Note: "Target lesion" is the lesion with the greatest diameter

Figure 1: Probability of ≥ Grade 3 hyperbilirubinemia and normal tissue absorbed dose



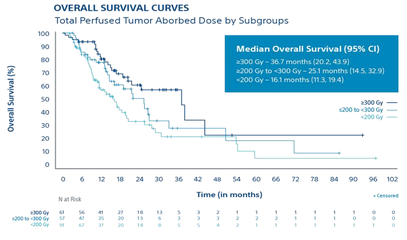
- Objective was to determine relationship between NTAD and ≥ Grade 3 hyperbilirubinemia in the absence of disease progression
- Too few patients (n=10) experienced ≥ Grade 3 hyperbilirubinemia to determine a relationship with NTAD (p=0.6 by logistic regression)
- Only 4.8% of patients (10/209) experienced such an AE

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



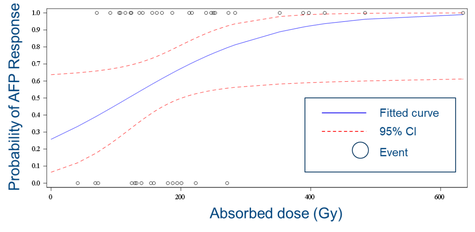
- ORR (mRECIST) was 61.7% over all lesions (129/209; 95% CI = 55.0%, 68.0%)
- ORR (mRECIST) was 70.8% for the target lesion (148/209; 95% Confidence Interval [CI] = 64.3%, 76.6%)
- Responders (n=129) had a significantly higher geometric mean TAD (225.5 Gy: 95% CI = 201.0 Gy, 253.0 Gy) compared with non-responders (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 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
- Total perfused TAD was significantly associated with AFP response at 90 days post-treatment (p=0.046 by logistic regression)

Discussion

- Large study population evaluated such that a range of NTAD and TAD could be studied to identify relevant thresholds for targeting safety and efficacy objectives
- Lack of association between occurrence of ≥ Grade 3 hyperbilirubinemia and NTAD denotes the safety of the treatment, in patients treated per instruction for use recommendation
- The range of TAD values evaluated supports the correlation between higher TAD and improved patient outcomes
- 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 occurrence of ≥ Grade 3 hyperbilirubinemia and NTAD
  - Low incidence confirms safety, demonstrates room for optimization for TAD
- TAD associated with better overall survival
  - This is in line with recently published results showing that higher TAD leads to longer survival
- Dose-efficacy relationship established (imaging and tumor-marker response)
  - Increased probability of tumor response and AFP response with higher TAD

Conflict of Interest Declaration

Disclosures: M.L. is a consultant for Boston Scientific and Terumo and recieves research support from Boston Scientific and Terumo. The department of Radiology and Nuclear Medicine at University Medical Center Utrecht receives royalties from Terumo.

For questions, please contact Marnix Lam at M.Lam@umcutrecht.nl

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