A prospective, multicenter, open-label, clinical trial design to evaluate the safety and efficacy of Y90 resin microspheres for treatment of unresectable hepatocellular carcinoma (HCC): Duration Of Objective Response with arterial Yttrium-90 (DOORwaY^{90})

DOORwaY-90 Study

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Objective:
To evaluate the safety and efficacy of SIRT using Y90 resin microspheres as first-line treatment for HCC in patients with Barcelona Clinic Liver Cancer (BCLC) stage A, B1, B2, and C.

Introduction

- Hepatocellular carcinoma (HCC) is often diagnosed when potentially curative resection or transplantation is not feasible.[1,2]
- Selective internal radiation therapy (SIRT) with Y90 resin microspheres (SIR-Spheres®) is an established locoregional treatment option for unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic chemotherapy of floxuridine in the US.
- SIRT has the potential to deliver a lethal dose of radiation to hepatic tumors, while sparing surrounding healthy liver tissue.[3,4]
- As an advance on previous SIRT trials in HCC,[5-7] DOORwaY^{90} is a US registration trial designed to utilize and delineate personalized dosimetry for treatment planning with Y90 resin microspheres.
- DOORwaY^{90} is a pivotal, prospective, multicenter, open-label single arm study designed to evaluate the safety and efficacy of Y90 resin microspheres as first-line treatment in patients with unresectable or unablatable HCC (Clinical trial registry number: NCT04736121).
- Important aspects of the study include:

- Personalized dosimetry for treatment planning - mean target dose to tumor is between 150-400 Gy
- Centralized review of the treatment plans and verification scans
- Use of an independent core laboratory for response assessment
- A specific patient population that would benefit from locoregional treatment
- Confirmation of absorbed dose delivered to the tumor using Y90 SPECT/CT or Y90 PET/CT
- Assessment of long-term toxicity

Methods

- All relevant institutional and local ethics committee approvals were gained before commencing the study.
- Written informed consent is obtained from all participants (or their legally authorized representatives) before participation in this study.
- Patient enrollment was initiated in March 2021 with the aim of recruiting 100 patients.
- The study is currently ongoing and is being conducted in 14 investigational sites in the USA. No single site will enroll more than 20% of the study population.
- Eligibility criteria have been recently revised to expand population since initial publication of paper in 2022.[8] Key patient inclusion and exclusion criteria are shown in Figure 1, with revisions marked in bold text.
- All recruited patients received SIRT with Y90 resin microspheres according to the general scheme outlined in Figure 2.

Figure 1: Patient inclusion and exclusion criteria.

Inclusion criteria

- ≥18 years old
- ≥6 months life expectancy
- HCC diagnosis with LI-RADS 4 or 5, or by histology
- Treatment naïve (**exceptions are: new lesions ≥6 months after liver resection with negative margins and no recurrence within 6 months; ablation of a single ≤3 cm lesion with no recurrence within 6 months**)
- BCLC stage A, B1, B2 and C with maximal single tumor size ≤8 cm and maximal sum of the tumor dimensions ≤12 cm
- At least 1 lesion **≥1 cm** in diameter (long axis) according to mRECIST
- Child-Pugh score A5 or A6
- ECOG performance score of 0 or 1
- ≥33% of liver volume disease free
- Adequate blood count, liver enzymes and renal function

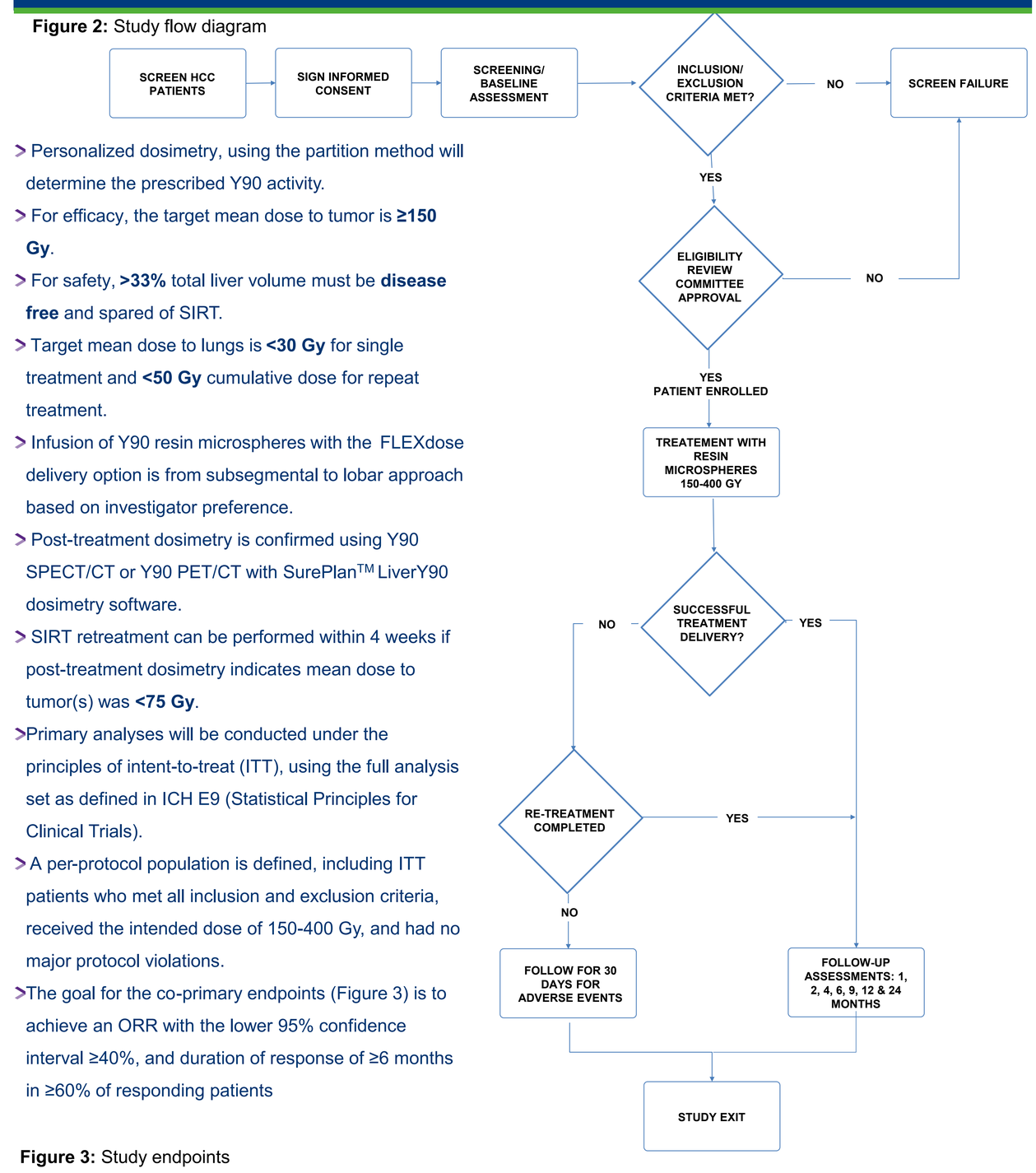
Exclusion criteria

- Patient eligible for ablation or resection for their malignancy in the opinion of the investigator at screening visit
- Prior systemic anti-cancer therapy (including immunotherapy and/or targeted therapy), radiotherapy or use of other investigational agents for the treatment of HCC
- Intrahepatic arteriovenous shunting
- Portal vein thrombosis
- Extrahepatic disease
- Contraindications to angiography
- Evidence of extrahepatic collateral supply to tumor
- Prior liver resection and/or transplant
- Planned localized cancer treatment to the liver or systemic cancer treatment, other than the study treatment, during the study.

Conclusion:
The DOORwaY^{90} trial is designed to assess the efficacy and safety of SIRT with Y90 resin microspheres as first-line therapy for unresectable HCC, using a personalized dosimetry approach.

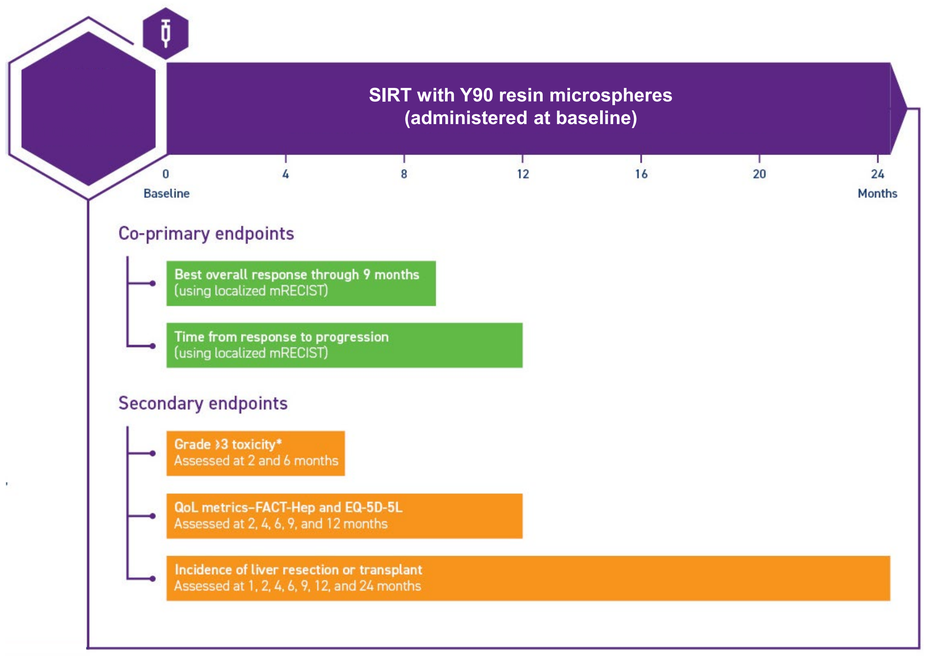
Methods (contd.)

Figure 2: Study flow diagram



- Personalized dosimetry, using the partition method will determine the prescribed Y90 activity.
- For efficacy, the target mean dose to tumor is **≥150 Gy**.
- For safety, **>33%** total liver volume must be **disease free** and spared of SIRT.
- Target mean dose to lungs is **<30 Gy** for single treatment and **<50 Gy** cumulative dose for repeat treatment.
- Infusion of Y90 resin microspheres with the FLEXdose delivery option is from subsegmental to lobar approach based on investigator preference.
- Post-treatment dosimetry is confirmed using Y90 SPECT/CT or Y90 PET/CT with SurePlan™ LiverY90 dosimetry software.
- SIRT retreatment can be performed within 4 weeks if post-treatment dosimetry indicates mean dose to tumor(s) was **<75 Gy**.
- Primary analyses will be conducted under the principles of intent-to-treat (ITT), using the full analysis set as defined in ICH E9 (Statistical Principles for Clinical Trials).
- A per-protocol population is defined, including ITT patients who met all inclusion and exclusion criteria, received the intended dose of 150-400 Gy, and had no major protocol violations.
- The goal for the co-primary endpoints (Figure 3) is to achieve an ORR with the lower 95% confidence interval ≥40%, and duration of response of ≥6 months in ≥60% of responding patients

Figure 3: Study endpoints



Discussion

DOORwaY^{90}: how it may add to our understanding?

1. The use of Y90 resin microspheres with personalized dosimetry as first-line therapy for HCC may strengthen future consensus guidelines
2. As the first US study in HCC using personalized dosimetry, DOORwaY^{90} provides clinically relevant and novel information on the efficacy & safety of Y90 resin microspheres
3. Increases evidence of Y90 SIRT with resin microspheres to downstage/bridge HCC patients to transplantation
4. If co-primary endpoints are met, personalized SIRT may potentially facilitate liver resection or transplantation in when used as first-line treatment in unresectable HCC patients

References

[1]Dimitroulis, et al: World J Gastroenterol 2017, 23:5282-5294; [2]El-Serag, et al: J Hepatol 2006, 44:158-166; [3]Kennedy, et al: Int J Radiat Oncol Biol Phys 2004, 60:1552-1563; [4]Arii, et al: J Hepatobiliary Surg 2003, 10(3):189-194; [5]Vilgrain, et al: Lancet Oncol 2017,18:1624-36; [6]Chow, et al: J Clin Oncol 2018, 36:1913-21; [7]Ricke, et al: J Hepatol 2019, 71:1164-74; [8]Mahvash, et al: BMC gastroenterology 2022, 22:151.

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