Overview of Ongoing Clinical Trials on Radioembolization

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The role and data driven basis for radioembolization remains ill-defined with recent phase III randomized trials negative for patients with hepatocellular carcinoma (HCC), and only a single second line trial in metastatic colorectal cancer (CRC) meeting its primary endpoint progression-free survival (EPOCH, NCT01483027) [1]. Few studies are currently underway to define and/or clarify the role of radioembolization. The search term “radioembolization OR SIRT OR TheraSphere OR TARE” (status: Aug. 2022), revealed 44 clinical trials at clinicaltrials.gov, of which only 25 are currently recruiting. However, additional active trials can be found in registries such as the European Union’s register EudraCT (2 additional active trials) [2] or national such as the German DRKS (3 additional active trials) [3]. Stratifying ongoing clinical trials as published in PubMed or clinicaltrials.gov, the following categories can be defined: (a) clinical trials evaluating the efficacy of SIRT in different tumor biologies metastatic to or primaries of the liver; as the most important subgroup, evaluation of combination therapies with systemic treatment, predominantly combining with checkpoint inhibition, including basic research seeking immune-modulating mechanisms and proof in tissue or blood; (b) assessing new technologies such as Holmium-166 for SIRT; and (c) new approaches (e.g., highly selected patient group) and indications for SIRT, also outside the liver.

The only phase III trial ongoing likely is STOP-HCC (NCT01556490), with advanced HCC patients receiving sorafenib ± radioembolization. Primary endpoint is overall survival, results are expected for end of 2022. However, this concept may come late given most recent developments in systemic HCC treatment shifting to immune checkpoint inhibition [4, 5]. Considering the presumptive immunomodulatory effect of radioembolization such combination therapies might be the future domain of radioembolization, which is supported by the results of a recently published phase II study from Singapore (NCT03033446, radioembolization + Nivolumab) [6] as well as by the promising preliminary results of a phase I (NCT03099564, radioembolization + Pembrolizumab) [7] and phase II study (NCT03380130, radioembolization + Nivolumab) [8]. Therefore, phase II trials such as IMMUWIN (NCT04522544; randomized, radioembolization or transarterial chemoembolization [TACE] combined with Durvalumab/Tremelimumab, primary endpoint objective response rate [ORR], completion 2024), SOLID (NCT04124991; single arm, radioembolization + Durvalumab, time-to-progression, completion 2022) or ROWAN (NCT05063565; randomized, radioembolization alone vs. radioembolization + Durvalumab/Tremelimumab, ORR, completion 2026) are of utmost interest for positioning radioembolization in HCC future treatment strategies. Recently evolved, the ZUGSPITZE trial, may add mechanistic as well as conceptual data through an extensive basic research program (EudraCT 2020-003,925-42, Sponsor LMU München, randomized three arm study, radioembolization standard vs. personalized dose + Durvalumab/Tremelimumab vs.checkpoint first followed by radioembolization on demand, endpoint ORR, completion estimated 2025). Further Phase II single arm studies combining radioembolization and immune checkpoint inhibition target cholangiocellular carcinoma (IMMUWHY, NCT04238637), CRC (SIRTCI, NCT04659382; iRE-C,
| Status                | Register number | Short title | Official study title                                                                 | Tumor                  | Primary endpoint | Study start date | Comment                                                                 |
|-----------------------|-----------------|-------------|--------------------------------------------------------------------------------------|------------------------|------------------|------------------|-------------------------------------------------------------------------|
| active, recruiting    | NCT02936388     | SirTac      | A Randomized Phase II Trial of RE With Yttrium-90 (SIRT) in Comparison with Transarterial Chemoembolisation With Cisplatin (TACE) in Patients With Liver Metastases From Uveal Melanoma | Uveal melanoma LM     | PFS              | 01/2016          | Only trial on Uveal melanoma metastases                                |
|                       | DRKS00009744     | AROMA       | Distant effects of radioembolization of hepatic malignancies on nonirradiated tumor tissue | CLM                    |                  | 03/2016          | Basic research/tumor biology                                           |
|                       | NCT03059030     | Yttrium-90 RE for Cirrhosis-Associated Thrombocytopenia |                             | CLM                    | OS               | 03/2017          | New indication                                                         |
|                       | NCT0327482      | DOSEY90     | Accurate Dosimetry and Biomarkers Improve Survival in HCC Patients Treated With Resin 90 Yttrium-Microspheres: A Randomized Trial | HCC                    | OS               | 04/2018          | Trial on dosimetry                                                     |
|                       | NCT03457948     | A Pilot Study of Pembrolizumab and Liver-Directed Therapy or Peptide Receptor Radiomimetic Therapy for Patients With Well-Differentiated NETs and Symptomatic Metastases | NET LM                 | BOR                   | 08/2018          | RE + immune checkpoint inhibition                                      |
|                       | NCT0362436      | ArTisaN     | A Phase II Assessment of the Safety and Efficacy of TheraSphere® SIRT in the Treatment of Metastatic (Liver) NETs | NET LM                 | ORR, AE incidence | 01/2019          | Trial on NET metastases                                                |
|                       | NCT0428637      | IMMUWHY     | Phase II Study of Immunotherapy With Durvalumab (MEDI4736) or Durvalumab and Tremelimumab, Both Combined With Y-90 SIRT in Advanced Stage ICC | ICC                    | ORR              | 11/2019          | RE + immune checkpoint inhibition                                      |
|                       | DRKS00021723    | POEM        | Study on feasibility and dose finding of SIRT with Y-90 microspheres in patients with malignant primary or secondary lung tumors | Any primary or secondary lung malignancy |                  | 06/2020          | New indication                                                         |
|                       | NCT04108481     | iRE-C       | Immunotherapy Combined With Yttrium-90 RE in the Treatment of Colorectal Cancer With Liver Metastases | CLM                    | MTD              | 10/2020          | RE + immune checkpoint inhibition                                      |
|                       | NCT04659382     | SIRTCI      | A Prospective, Multi-center, Open-label, Phase II Study to Evaluate Efficacy and Safety of SIRT Plus Cisplatin, Bevacizumab and Tremelimumab in Patients With Liver-dominant Metastatic Colorectal Cancer | CLM                    | PFS              | 10/2020          | RE + immune checkpoint inhibition                                      |
|                       | NCT04541173     | IMMUWIN     | A Randomized Phase II Study of Atezolizumab and Bevacizumab With Y-90 TARE in Patients With Unresectable HCC | HCC                    | PFS              | 11/2020          | RE + immune checkpoint inhibition                                      |
|                       | NCT04522544     | IMMUWIN     | A Phase II Study of Immunotherapy With Durvalumab (MEDI4736) and Tremelimumab in Combination With Either Y-90 SIRT or TACE for Intermediate Stage HCC With Pick-the-winner Design | HCC                    | ORR              | 12/2020          | RE + immune checkpoint inhibition                                      |
|                       | NCT04607531     | IMMUWIN     | A Phase Ib Study of Durvalumab (MEDI4736) and Tremelimumab Following RE in Patients With Unresectable Locally Advanced HCC | HCC                    | Overall response rate, DLT, AE Incidence | 08/2021          | RE + immune checkpoint inhibition                                      |
|                       | NCT0439035      | CapTemY90   | UPCC 04,219 Phase 2 Study of Capcitabine-Temozolomide(CapTem) With Yttrium-90 RE in the Treatment of Patients With Unresectable Metastatic Grade 2 NETs | NET LM                 | hepatic PFS      | 10/2021          | Trial on NET metastases                                                |
|                       | NCT05265208     | SIROCHOCO   | A Multi-center Open-label Randomized Controlled Prospective Phase II Study Evaluating the Efficacy of SIRT (Yttrium-90 Glass Microspheres) Combined With Capcitabine in the Neoadjuvant Setting of Operable ICC | ICC                    | Frequency of subjects with adequate surgical margins | 02/2022          | Trial on ICC                                                           |
|                       | DRKS00009916     | SWARM       | Systemic release of growth factors after RE of hepatic malignancies | Any primary or secondary hepatic malignancy |                  | 03/2022          | Basic research/tumor biology                                           |
|                       | NCT05063565     | ROWAN       | An Open-Label, Prospective, Multi-Center, Randomized Clinical Trial to Evaluate The Efficacy and Safety Of TheraSphere Followed by Durvalumab (Immitiz®) With Tremelimumab vs. TheraSphere Alone For HCC | HCC                    | ORR, DoR          | 08/2022          | RE + immune checkpoint inhibition                                      |
Table 1 continued

| Status                | Register number | Short title | Official study title                                                                 | Tumor          | Primary endpoint | Study start date | Comment                                      |
|-----------------------|-----------------|-------------|---------------------------------------------------------------------------------------|----------------|-----------------|------------------|---------------------------------------------|
| active, not recruiting| NCT01556490     | STOP-HCC    | A Phase III Clinical Trial of Intra-arterial TheraSphere in the Treatment of Patients With Unresectable HCC | HCC            | OS              | 03/2012          | Only phase III trial                          |
|                       | NCT02807181     | SIRCCA      | Prospective, Multicenter, Randomized, Controlled Study Evaluating SIR-Spheres Y-90 Resin Microspheres Preceding Cisplatin-gemcitabine (CIS-GEM) Chemotherapy vs. CIS-GEM Chemotherapy Alone as First-line Treatment of Patients With Unresectable ICC | ICC            | Survival at 18 months | 01/2017          | First-line unresectable ICC                  |
|                       | NCT03099564     | HCRN        | A Pilot Study of Pembrolizumab in Combination With Y90 RE in Subjects With Poor Prognosis HCC With Preserved Liver Function | HCC            | PFS             | 03/2017          | RE + immune checkpoint inhibition             |
|                       | NCT03812562     |             | Pilot Study of Nivolumab in Combination With Therasphere (Yttrium-90) for Treatment of HCC With Intent for Resection | HCC            | Recurrence rate | 02/2019          | RE + immune checkpoint inhibition             |
|                       | NCT04124991     | SOLID       | A Single-arm, Open-label, Safety and Efficacy Study of RE With Yttrium-90 Microspheres in Combination With Durvalumab (MED14736) in Locally Advanced and Unresectable HCC | HCC            | TTP             | 06/2020          | RE + immune checkpoint inhibition             |
|                       | 2020-003925-42  | Zugsipitze  | A randomized open-label phase II study on the effect of durvalumab and tremelimumab combined with personalized SIRT, standard-dose SIRT or immunotherapy followed by on-demand loco-regional SIRT in non-resectable HCC patients | HCC            | ORR             | 10/2021          | RE + immune checkpoint inhibition and dosimetry |
|                       | NCT05141448     | iHEPAR      | Individualized Dosimetry for Holmium-166-RE in Patients With Unresectable HCC; a Multi-center, Interventional, Non-randomized, Non-comparative, Open Label, Early Phase II Study | HCC            | Rate of unacceptable toxicity | 11/2021 | Holmium-166, dosimetry |
|                       | NCT05092880     | CAIRO7      | RE in Elderly/Fragile Patients With Unresectable Livermetastases of Colorectal Cancer | CLM            | PFS             | 11/2021          | Highly selected patient cohort                |
|                       | NCT05327738     |             | A Phase II Study to Evaluate the Efficacy and Safety of Y-90, Atezolizumab and Cabozantinib Among Patients With Unresectable and Locally Advanced HCC | HCC            | Proportion of progression-free participants | 06/2022 | RE + immune checkpoint inhibition             |
|                       | NCT05303467     | FRONTIER    | A Feasibility Study to Evaluate the Safety of the TheRaSphere Glioblastoma (GBM) Device in Patients With Recurrent GBM | GBM            |                 | 07/2022          | New indication                                |
|                       | NCT05377034     | STRATUM     | A Multinational, Double-blind, Placebo-Controlled, Parallel Randomized Arms, Phase II Trial to Compare Safety and Efficacy of SIRT (Y-90 Resin Microspheres) Followed by Atezolizumab Plus Bevacizumab vs. SIRT Followed by Placebo in Patients With Locally Advanced HCC | HCC            | BOR             | 07/2022          | RE + immune checkpoint inhibition             |
|                       | NCT05315687     |             | Safety and Efficacy of RE of Metastatic Breast Cancer to the Liver as a 2nd/3rd Line Therapy | BCLM           | PFS             | 07/2022          | Trial on breast cancer metastases             |
|                       | NCT05422690     |             | A Phase II Trial of Induction Gemcitabine, Cisplatin and Nab-Paclitaxel Triplet Chemotherapy Followed by Gemcitabine, Cisplatin and RE for the Treatment of Locally Advanced Unresectable ICC | ICC            | ORR             | 07/2022          | Trial on ICC                                  |
|                       | NCT05451862     | HOMIE-166   | Holmium-166 Transarterial RE in Unresectable, Early Stage HCC; a Prospective, Single-arm, Open Label, Multicenter Phase II Study | HCC            | ORR             | 12/2022          | Holmium-166                                  |
|                       | NCT05195710     |             | Preoperative Y-90 RE for Tumor Control and Future Liver Remnant Hypertrophy in Patients With Colorectal Liver Metastases | CLM            | Feasibility and safety | 05/2023 | New indication                                |

AE, adverse event; BCLM, Breast cancer liver metastases; BOR, Best observed overall response rate; CLM, Colorectal liver metastases; DLT, Dose-limiting toxicity; DoR, Duration of Response; GBM, Glioblastoma; HCC, Hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; LM, liver metastases; MTD, maximum tolerated dose; NET, neuroendocrine tumor; ORR, Objective response rate; PFS, Progression-free survival; RE, radioembolization; TTP, Time to progression
NCT04108481) or neuroendocrine tumors (NCT03457948). Finally, the only active clinical cancer trial for non-liver indications seems to be POEM (DRKS00021723), a phase I/II trial assessing safety and efficacy as a composite endpoint when using the bronchial arteries to target primary or secondary lung malignancies. Completion is expected 2023. Table 1 provides a selected overview of currently ongoing trials with comments regarding the crucial characteristics of each study.

In summary, only a small number of clinical trials are currently active, almost all limited to small Phase II concepts. Given the lack of comprehensive data on the clinical benefit of radioembolization, emerging data clearly will not suffice to secure radioembolization as integral part of future treatment strategies and guidelines.

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Declarations

Conflict of interest Jens Ricke declares consulting, advisory arrangements, and research grants and travel grants from Sirtex Medical, and consulting, advisory arrangements and receiving travel grants from BTG. Matthias P. Fabritius has no conflicts of interest to declare.

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