Q&A

Contents

1. General 2
2. Technical 3
3. Logistics 3
4. Clinical & Safety 4
5. Q-accessories 7
   5.1 Q-Suite 7
   5.2 Q-Scout 8
6. References 8

1. General

What is the incidence and mortality of liver cancer?

Primary liver cancer is globally the sixth most frequent cancer, and the second leading cause of deaths from cancer. In 2012 it affected 782,000 people and resulted in 746,000 deaths.[1]

A similar number of patients die from liver metastatic disease and secondary, metastatic malignancies in the liver. Unfortunately, treatment options are still limited and in consequence, the mortality-over-incidence ratio is very high at 0.93.

In what countries is QuiremSpheres® available?

QuiremSpheres® is available in most European countries. Terumo Europe will be the exclusive distributor of QuiremSpheres®. Outside Europe, QuiremSpheres® is only on sale in selected countries.

I am interested in using QuiremSpheres®. Who can I contact?

Please contact your local Terumo representative.

What is the relationship between Terumo and Quirem Medical?

Terumo acts as the exclusive global distributor of QuiremSpheres®. QuiremSpheres® is manufactured by Quirem Medical.

I am using an yttrium-based SIRT product. Why should I be interested in QuiremSpheres®?

QuiremSpheres® has the same mode of action as yttrium-based SIRT products: it emits beta radiation to kill tumour cells. In addition, QuiremSpheres® can be visualized with SPECT, due to γ-radiation, and MR imaging, as it is paramagnetic, even in low concentrations. This is unique and cannot be achieved with currently available yttrium microspheres. QuiremSpheres® will come with a proprietary software tool called Q-Suite, used to calculate the absorbed dose based on the SPECT and MR images. This allows post-treatment evaluation of the size of the dose delivered to the individual tumours and non-target tissue.

Will QuiremSpheres® be reimbursed?

Please contact your local Terumo representative for more information on the reimbursement options available in your market.

What are the costs (per vial) compared to Y-90?

Please contact your local Terumo representative for more information on the price of QuiremSpheres® and Q-Suite.

2. Technical

What is the work-up procedure for QuiremSpheres®?
The work-up procedure is identical to that used for Yttrium-90 SIRT, i.e. the safety of the SIRT is evaluated based on a Tech-99m MAA procedure.

Can I order multiple doses per patient?
Yes, we support multiple customized doses per patient for lobar or segmental treatment.

How are QuiremSpheres® administered?
QuiremSpheres® are administered using the QuiremSpheres® re-usable Customer Kit and disposable Delivery Sets. Please visit the Terumo booth for a demo.

How is the required activity of QuiremSpheres® calculated?
Calculation of the activity of QuiremSpheres® is based on the MIRD model. For more information, see the instructions for use of QuiremSpheres®.

3. Logistics

How can I order QuiremSpheres® once it is available?
You can order QuiremSpheres® through your local Terumo Europe sales representative. A patient order needs to be received 7 calendar days prior to the scheduled treatment day.

Our department wants to start using QuiremSpheres®. What action do we need to take? Please contact your Terumo representative. We will fully support you in the process of preparing for and executing your first QuiremSpheres® patient treatment. One of the first steps is to ensure all local regulations and requirements are met for working with holmium-166. In most cases, this means a holmium permit needs to be requested from the local authorities.

How is QuiremSpheres® supplied?
QuiremSpheres® is provided as a patient-specific product with custom activity. It can be supplied in multiple vials or as a 'split dose' for lobar or segmental treatment.

How long can QuiremSpheres® be used after being delivered to the hospital?
Example: QuiremSpheres® is ordered as a dose of 4 GBq to be administered on a Tuesday morning at 11 am. It is delivered to the hospital at 6am with an activity of 4.6 Gbq to account for decay. Accepting a 5% deviation from the planned activity, the therapeutic window ranges from 9 am (4.2 Gbq) until 1 pm in the afternoon (3.8 GBq).

4. Clinical & Safety

Are there side effects of treatment with QuiremSpheres®?

The most common adverse events are similar to those observed after yttrium-90 SIRT during follow-up: nausea and vomiting, abdominal pain, fever, mild to moderate abnormality of liver function tests and diarrhoea. In a phase II trial conducted at the UMCU, holmium-166 radioembolization decreased the global health status temporarily from 83 at baseline to 42 after 1 week. It recovered after 6 weeks.[2] For more information, we refer to the QuiremSpheres® instructions for use.

Will the (low-energy) gamma radiation cause an additional radiation burden to the clinical staff?

The low-energy gamma radiation component does not add significantly to the total dose exposure of the SIRT treatment. The QuiremSpheres® product packaging and the QuiremSpheres® Customer Kit (administration box) are designed with Perspex® and lead shielding to reduce radiation exposure when preparing and performing the procedure. In addition, since the suspension step is performed by Quirem Medical, dose exposure to clinical staff is further reduced.

Are there contact restrictions for patients treated with QuiremSpheres®?

No contact restrictions are necessary for patients who are discharged 6 hours after treatment and who received < 7GBq.[3]

What is the Intended Use according to the instructions for use?

QuiremSpheres® is intended for implantation in hepatic tumours via the hepatic artery.[2]

Do you provide a system for administration of QuiremSpheres®?

Yes, we will provide your hospital with two re-usable QuiremSpheres® Customer Kits. The sterile QuiremSpheres® Delivery Sets can be ordered separately when ordering a QuiremSpheres® patient dose.

What doses are available for ordering (range of activity)?

QuiremSpheres® is a patient-specific product, meaning that it is custom-made and the activity matches the activity required for the patient treatment planned. Typically, the activity ranges between 4 and 10 GBq.

Can you merge/combine antibodies with holmium? (Erbium)

Research has been done on combining antibodies with holmium, see Thompson et al.[4] and Khorami-Moghadam et al.[5]. Theoretically it is possible to also label the microspheres. However, it is to be expected that, due to the size of the microspheres, physical and rheological properties will overcome the effect of targeting with antibodies.

Do we have to perform interventions in MR with holmium in the future?
Holmium microspheres can be visualized with SPECT and MR imaging. The unique ability of holmium microspheres to be visualized with magnetic resonance essentially enables real-time MR-guided administration of microspheres. However, the clinical applicability and possible advantages of such an approach are subject to further research.

What if you need to perform a second treatment? How is it possible to distinguish between old and new spheres (in MRI)?
If the second treatment does not involve the target volume of the first treatment, detection and quantification can be done per specific area by means of segmentation.
For a second treatment involving the same target volume, there are two possibilities for evaluating and quantifying the newly administered microspheres.
By making a pre-treatment MR image after the first but prior to the second treatment a new baseline measurement is created for the second treatment. This new baseline can be visually compared to the post-treatment images of the second treatment to detect the newly deposited microspheres.
Assuming the time between both treatments was long enough for the microspheres first introduced to fully decay, SPECT can be used instead of MR to evaluate the in vivo microsphere distribution. Only the microspheres introduced second will emit photons and be detectable.

Which is the current model for calculating the dose (partition model)?
For QuiremSpheres® the MIRD (Medical Internal Radiation Dose) model is used, aiming for a 60Gy mean dose to targeted liver volume. Due to the preferential flow of microspheres to the tumours, generally a much higher dose (typically exceeding 100Gy) is absorbed by the tumour tissue and a lower absorbed dose delivered to the healthy tissue.

When do you recommend performing the Tech-99m MAA scan?
QuiremSpheres® needs to be ordered 7 days prior to the date planned for treatment. Typically, the Tech-99m MAA scan is performed before placing the order.

Are studies aiming for “better treatments” or for “non-inferiority”?
The HEPAR 2 study, which was a phase-2 efficacy study, showed similar performance to yttrium-90 microspheres. It should be noted that in this study the imaging capabilities of holmium-166 microspheres were not used to improve the treatment outcome. It may be expected that by using the imaging capabilities of QuiremSpheres®, more targeted treatment will be possible, driving the treatment outcome. At this point in time, we are designing our future clinical trials programme.

Is this procedure suitable for non-liver centre hospitals?
QuiremSpheres® is indicated for advanced unresectable liver cancer only. Since SIRT is a complex procedure, it is recommended only starting to use SIRT if your hospital has the patient volume to build and maintain the required skills.

Can the results of Y-90 be extrapolated to Ho-166?
Both QuiremSpheres® as well as yttrium microspheres use beta radiation as the key mode of action for treating liver malignancies. To that end, the absorbed dose determines the lesions response. Therefore, on a fundamental level, the results of yttrium microspheres can be extrapolated. We do believe, however, that since QuiremSpheres® offers unique possibilities for verifying the treatment, SIRT outcome can be further improved. QuiremSpheres® enables you to see what you treat, and treat what you see.

Is it possible to visualize and quantify the intrahepatic distribution of holmium microspheres?
Yes, by using standard SPECT and MR imaging equipment for in vivo imaging of the microspheres the intrahepatic distribution of the microspheres can be visualized and quantified. The images can be converted to 3D quantitative dose distributions using the Q-Suite software package.

What is your rate of neutropaenia? How will you deal with that in patients receiving immunotherapy?
In the Hepar 1 study it was concluded that biochemical toxicity, consisting of grade 1–2 increases in ALT, AST, and bilirubin serum concentrations, grade 1–2 hypoalbuminaemia, and grade 1–3 increase of gamma-glutamyltransferase and lactate dehydrogenase concentrations, was in line with the toxicity reported for ^{90}Y-radioembolisation[6].

What is the cumulative toxicity of PRT + QuiremSpheres® in NET?
This is currently under investigation in the Hepar Plus study. This study is expected to report the outcome in late 2018.

Are there any examples of dose escalation? In other words, how high can you go? To what extent is that different to Y-90?
In Hepar 1, which was a dose escalation trial, it was shown that 60 Gy was the maximum tolerated mean dose to the whole liver. Pre-clinical work shows that the dose can be further escalated both for holmium-166 and yttrium-90[8].

Do you think that treatment could be done on the same day as assessment (MAA)?
At the University Medical Center Utrecht work-up of the patient by means of a scout dose of holmium microspheres and therapeutic treatment is done on the same day. The patients are kept in overnight for their own comfort, but in terms of radiation hygiene the patients are allowed to go home the same day.

How long does the paramagnetic effect of holmium last?
The paramagnetic effect is a characteristic of the element Ho-165 and only a fraction (less than 0.1%) of Ho-165 is activated to Ho-166 on production (and which decays to erbium-166). This means that the paramagnetic effect will remain, also after the QuiremSpheres® have decayed.

Can we use the radio-opacity of the spheres for follow-up images?
The radio-opaque effect of QuiremSpheres® microspheres is not sufficient to be used in a quantitative way for follow-up due to the limited concentration of microspheres. However, the microspheres can be quantitatively imaged with SPECT and MR imaging, due to paramagnetic properties of holmium and gamma radiation. New developments in CT imaging, such as dual-energy CT, may enable CT imaging of QuiremSpheres® in the future.

How does QuiremSpheres® perform in liver malignancies?
In the HEPAR 2 trial performed at the University Medical Center Utrecht, efficacy was shown for the treatment of metastatic liver cancer with holmium microspheres. The efficacy is similar to yttrium-90 microspheres, as known from literature[10].

What protection is recommended to minimize the radiation burden from the γ-radiation?
The gamma radiation emitted by QuiremSpheres® is of low energy (81 KeV) and is therefore easily shielded by common protective angio-suite clothing (lead apron, thyroid shield, etc.). In addition, the gamma radiation exposure due to QuiremSpheres is only a fraction of the exposure due to x-rays from fluoroscopic or cone beam CT imaging during an angiographic procedure[11] .

Is PLLA absorbed or permanent?
PLLA is a biodegradable material. However, no noteworthy macroscopic effect will occur within the first year. After this period, the polylactate will form lactate and most of the holmium will form a complex with lactate and remain in the liver[12,13] .

Does QuiremSpheres® embolize?
The size of the microspheres (30 micron) is such that they will lodge in the microvasculature in and around the tumour lesions. This is typical of SIRT. Subsequently, the main mode of action of QuiremSpheres® is cell death due to beta radiation. Embolization of larger vessels is not to be expected due to the small size and low number of administered microspheres. However, it is advised to check for stasis and backflow during the administration procedure.

5. Q-accessories

5.1 Q-Suite

When will Q-Suite, the software tool for QuiremSpheres®, be available?
Q-Suite received CE in early 2017 and is available to QuiremSpheres® customers.

Is Q-Suite software compatible with all available machines (imaging) on the market?
Q-Suite is a Microsoft Windows desktop application that connects via the file sharing DICOM standard. This means that essentially, it is compatible with all imaging machines on the market. Q-Suite software should be installed on a Windows 7 or Windows 10 computer. However, because DICOM implementation differs from manufacturer to manufacturer, on installation of Q-Suite at a hospital site a compatibility test with the installed machines will be performed.

5.2 Q-Scout

Do you also provide a scout dose based on holmium-166 microspheres?

Currently, the use of a scout dose of holmium-166 microspheres is limited to clinical studies only. At this time no scout dose is commercially available. We expect this product to become available in 2018.

How will dose calculation be modified/improved by using a scout dose?

This is to be carefully explored in a clinical study setting once the scout dose becomes commercially available. For example, using the measured tumour to non-tumour ratio of the scout dose, the therapeutic dose to the tumours can be escalated while ensuring the dose to normal tissue remains within safety limits.

Is the scout dose standard or individualized?

The scout dose, which is expected to become commercially available in 2018, will contain a standard dose of microspheres and activity. It can be ordered split over multiple vials to simulate a lobar or segmental treatment approach.

6. References

1. World Cancer Report 2014. World Health Organization. 2014. pp. Chapter 1.1. ISBN 9283204298.
2. Package insert (IFU) QuiremSpheres® LS-1101-10.03, Issue date: 07-02-2017, Quirem Medical
3. Prince et al. (2014) Radiation emissions from patients treated with holmium-166 radioembolization; Journal of Vascular and Interventional Radiology.
4. Thompson *et al.*, "166Ho and 90Y labeled 6D2 monoclonal antibody for targeted radiotherapy of melanoma: Comparison with 188Re radiolabel," *Nucl. Med. Biol.*, vol. 41, no. 3, pp. 276–281, Mar. 2014.
5. A. Khorami-Moghadam, B. Bolouri, A. R. Jalilian, N. M. A. Bahrami-Samani, S. M. Mazidi, and B. Alirezapour, "Preclinical evaluation of holmium-166 labeled anti-VEGF-A(Bevacizumab)," *J. Label. Compd. Radiopharm.*, vol. 56, no. 8, pp. 365–369, Jun. 2013.
6. M. L. Smits *et al.*, "Holmium-166 radioembolisation in patients with unresectable, chemorefractory liver metastases (HEPAR trial): a phase 1, dose-escalation study," *Lancet Oncol.*, vol. 13, no. 10, pp. 1025–1034, Oct. 2012.
7. S. A. van Nimwegen *et al.*, "Intratumoral injection of radioactive holmium (166 Ho) microspheres for treatment of oral squamous cell carcinoma in cats," *Vet. Comp. Oncol.*, May 2017.
8. M. A. D. Vente *et al.*, "Clinical effects of transcatheter hepatic arterial embolization with holmium-166 poly(l-lactic acid) microspheres in healthy pigs," *Eur. J. Nucl. Med. Mol. Imaging*, vol. 35, no. 7, pp. 1259–1271, Jul. 2008.
9. A. F. van den Hoven, M. L. J. Smits, C. E. N. M. Rosenbaum, H. M. Verkooijen, M. A. A. J. van den Bosch, and M. G. E. H. Lam, "The Effect of Intra-Arterial Angiotensin II on the Hepatic Tumor to Non-Tumor Blood Flow Ratio for Radioembolization: A Systematic Review," PLoS One, vol. 9, no. 1, p. e86394, Jan. 2014.
10. J. F. Prince *et al.*, "Efficacy of radioembolization with holmium-166 microspheres in salvage patients with liver metastases: a phase 2 study.," *J. Nucl. Med.*, p. jnumed.117.197194, Sep. 2017.
11. J. F. Prince *et al.*, "Radiation Emission from Patients Treated with Holmium-166 Radioembolization," *J. Vasc. Interv. Radiol.*, vol. 25, no. 12, p. 1956–1963.e1, Dec. 2014.
12. S. W. Zielhuis, J. F. W. Nijsen, G. C. Krijger, A. D. van het Schip, and W. E. Hennink, "Holmium-Loaded Poly(l-lactic Acid) Microspheres: In Vitro Degradation Study," *Biomacromolecules*, vol. 7, no. 7, pp. 2217–2223, Jul. 2006.

13. S. W. Zielhuis *et al.*, “Long-term toxicity of holmium-loaded poly(l-lactic acid) microspheres in rats,” *Biomaterials*, vol. 28, no. 31, pp. 4591–4599, Nov. 2007.