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Eighteen-Months Safety and Efficacy Following Intraperitoneal Treatment With ^{224}Radium-Labeled Microparticles After CRS-HIPEC in Patients With Peritoneal Metastasis From Colorectal Cancer

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ABSTRACT

Background and Objectives: Peritoneal metastasis from colorectal cancer carries a high risk for relapse after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). A novel alpha-emitting radiopharmaceutical (Radspherin) has been designed to deliver short-range radiation to micrometastases and free-floating tumor cells.

Methods: A Phase 1/2a study evaluated the safety, tolerability, and signal of efficacy of escalating doses of Radspherin injected intraperitoneally after CRS-HIPEC.

Results: Eleven patients received 1–4 MBq (Group 1) whereas 12 patients received 7 MBq; nine patients single dose/three patients split-dose (Group 2). Median age was 66.5 and 61.5 years, and median peritoneal cancer index 6 and 7, respectively. One hundred and seventy-eight adverse events were reported, only seven were deemed related to Radspherin. Thirteen serious adverse events (SAEs) were reported in eight patients and no SAEs were related to Radspherin. At 18-months, none of the 12 patients receiving 7 MBq experienced peritoneal recurrences, however four had non-peritoneal recurrences. Across both groups ($n = 22$), 41% had recurrent disease, only 14% of them in the peritoneum.

Conclusions: Radspherin was well tolerated. At 18 months, median disease-free survival has not been reached, and none of the patients receiving the recommended dose (7 MBq) had peritoneal recurrences. The results are encouraging and warrant further clinical evaluation.

1 | Introduction

Colorectal cancer (CRC) presenting with peritoneal metastases (PM) represents a major challenge in disease management, marked by the intricate disease dynamics and therapeutic complexities, as well as the persistent threat of disease recurrence [1, 2]. Despite advancements in cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) as a curatively intended approach, a significant unmet need persists, as remaining free-floating cancer cells and micrometastases may subsequently develop into new overt metastases. The expected median time to progression after CRS-HIPEC is about 12 months [3, 4] and 5-year overall survival (OS) is reported in no more than 40% of cases [5–7].

Radspherin is a novel radiopharmaceutical for postoperative intraperitoneal (IP) administration after complete CRS. It is based on the delivery of short-range and cytotoxic alpha particles emitted during the decay of ^{224}Ra bound to slowly biodegradable calcium carbonate microparticles [8–10]. Alpha particles have high linear energy transfer and a radiation range of less than 100 μm (3–10 cell diameters), generating highly localized and dense ionizing radiation with predominantly non-repairable double-strand DNA breaks [11].

The 30-days short-term experience of the current study has previously been published and determined a dose of 7 MBq to be safe and the recommended activity dose of Radspherin to be used in further studies [8]. All doses were well tolerated with dose-limiting toxicity (DLT) not reached. No deaths occurred and none of the serious adverse events (SAEs) were considered related to Radspherin. The biodistribution of Radspherin showed good peritoneal distribution of the radiolabeled microparticles [8].

Fifteen months safety and efficacy were presented at American Society of Clinical Oncology (ASCO 2023, abstract number 3518). Here we present mature safety and survival data at the pre-specified 18 months end of study visit, also presented orally at the Peritoneal Surface Oncology Group International (PSOGI) congress in Venice, 2023.

2 | Materials & Methods

2.1 | Clinical Study & Patients

A Phase 1/2a study (EudraCT 2018-002803-33) has been completed in two dedicated CRS-HIPEC centers in Oslo, Norway and Uppsala, Sweden. A later amended and extended expansion cohort is ongoing.

The aim was to evaluate safety, tolerability, and signal of efficacy of Radspherin injected intraperitoneally 2 days after CRS-HIPEC. The dose escalation was performed by a standard 3 + 3 design with increasing dose levels starting at 1 MBq followed by 2, 4, and 7 MBq or until DLT eventually was observed. Furthermore, a repeated injection cohort was explored in three patients, where the recommended dose was split into two separate injections given 1 week apart. Additionally, an expansion cohort with six patients was included at recommended dose (7 MBq) from dose escalation part of the study [8]. Twenty-nine patients were screened, of whom 23 were included between May 11, 2020 and August 16, 2021 (Figure 1). Clinicopathological characteristics are shown in Table 1.

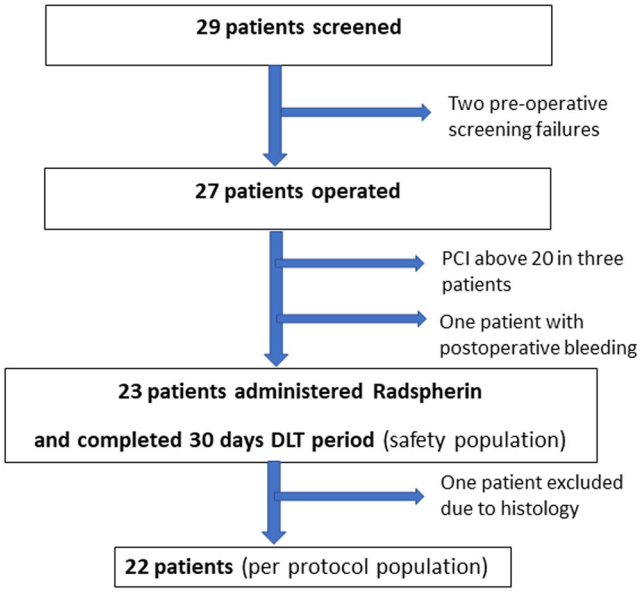

FIGURE 1 | Consort flow diagram of study patients (per protocol population, $n = 22$).

The study was approved by the National Ethics Committees in both Norway and Sweden, as well as the Norwegian Medicines Agency and the Swedish Medical Products Agency. Prospective data was registered in Sponsors database (Viedoc).

The primary objectives of the study were to investigate safety and toxicity of Radspherin, to determine a maximum tolerated dose (MTD) of Radspherin, among the four activity doses studied (1, 2, 4, and 7 MBq) given as IP injection 2 ± 1 days after CRS and HIPEC. The secondary objectives of the study were to establish a recommended dose of Radspherin as a single IP injection or two repeated IP injections following CRS and HIPEC, to describe the biodistribution of Radspherin and examine the efficacy and clinical benefit of Radspherin following CRS and HIPEC.

2.2 | Treatment Technique and Catheter Placement

CRS aimed to remove all macroscopically visible tumor, involving peritonectomy procedures and organ resections as deemed necessary. Peritoneal tumor distribution was classified using the peritoneal cancer index (PCI) [12] and the completeness of cytoreduction (CC) score [12] was used to document any residual tumor after CRS. Only the CC-0 cases were given HIPEC. Synchronous PM was defined as known metastases at diagnosis or within 6 months of primary surgery and disease-free interval (DFI) was the time period from primary surgery to diagnosis of PM [13]. Postoperative complications (30-day morbidity and mortality) were classified according to Accordion [14].

HIPEC was administrated using a closed technique with an open abdomen at the study site in Norway [15], whereas the closed abdomen technique was used in Sweden [16]. The HIPEC regimen contained Mitomycin, 35 mg/m^2 (maximum 70 mg) in Norway, administered for 90 min in three fractions (50% initially, 25% after 30 and 60 min, whereas in Sweden Oxaliplatin 460 mg/m^2 or Irinotecan 460 mg/m^2, both for 30 min) were given. The cytotoxic drugs were circulated in the abdominal cavity at a temperature of 42.0°C. An in-dwelling peritoneal Blake catheter was placed anteriorly in the upper abdominal cavity for administration of Radspherin.

According to prevailing national guidelines, adjuvant chemotherapy was not routinely given. However, in the cause of synchronous PM with locoregional lymph node metastasis, adjuvant chemotherapy was recommended after CRS-HIPEC/Radspherin, otherwise not.

Data were recorded in the eCRF, and external study monitoring and source data verification were performed. The study was reviewed by both a Safety Monitoring Committee and an Independent Data Monitoring Committee. Categorical variables were described using frequencies/percentages and continuous variables were described with median/range. Safety evaluations were based on the incidence, intensity and type of AEs, and clinically significant changes in the subjects' vital signs and clinical laboratory results. Survival outcomes were estimated using the Kaplan–Meier method, and curves compared using the log-rank test. OS was measured from the date of Radspherin injection until last follow-up visit after 12 months (1–4 MBq)/18 months (7 MBq) or date of death. Disease-free survival (DFS) and peritoneal recurrence-free survival (PRFS) were measured until the date for disease recurrence/peritoneal disease recurrence or end of study.

2.3 | Radspherin—a Novel Radiopharmaceutical

Radspherin microparticles are a type of radiation therapeutic for local treatment of IP cancer cells and micrometastases aiming to be administered at therapeutically effective radiation doses without causing harmful side effects. This radiopharmaceutical uniquely provides a nonsystemic, receptor-independent, and ultra-short-range radiation therapy.

The major features of Radspherin are; (I) a microparticle suitable for infusion into a body cavity, with a size promoting distribution and local cavity retention, and (II) alpha-emitting radionuclide attached to the microparticle irradiating the immediate surrounding of the microparticle. The microparticle is made mainly of calcium carbonate and, as such, slowly degradable into harmless cations and anions (9,10)...ref 11 is not correct, change to reffs 9 and 10 [11].

The alpha emitting radionuclide attached to the microparticle is ^{224}Ra with a half-life of 3.6 days that together with short-lived progenies produces four alpha particles per radium atom (Figure 2) [10].

An autoclaved suspension of Radspherin is administrated typically 2 days after surgery via a catheter and flushed with a biocompatible buffer for maximum dispersion in the peritoneal cavity.

Radspherin generates highly localized alpha-radiation with a range of less than 0.1 mm in tissue, thereby avoiding radiotoxic doses reaching sensitive tissues in the abdominal cavity. Also, the retention properties of the microparticles favors local dose deposition with practically insignificant systemic exposure. Radspherin was designed to be used after surgery in cancers where postsurgical peritoneal spread of cancer cells may be a problem, including, for example, colorectal-, gastric,- and ovarian cancer and abdominal mesothelioma. After the microparticles have lost their capacity for radiation, the calcium-carbonate-based carrier material is dissolved, absorbed, and naturally excreted by the body.

Dose-calibrated Radspherin (0.7–1.0 g microparticles, 1–7 MBq ^{224}Ra, 7–10 mL) was prepared by the study Sponsor, Oncoinvent AS, at their certified production facility, calibrated at the Hospitals' nuclear medicine departments and administered as

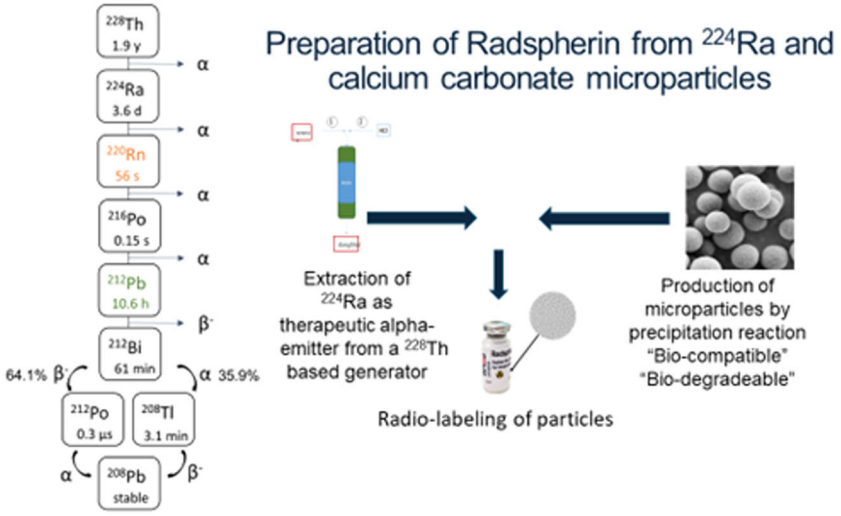

FIGURE 2 | Decay-scheme of radium 224. Manufacturing and properties of Radspherin. Radium-224 is prepared from a long-lived generator based on ^{228}Th (half-life of 1.9 years). The purified ^{224}Ra is thereafter used for radiolabelling of the calcium carbonate microparticles.

diluted slow bolus injection via the inserted peritoneal catheter. Thereafter the syringe and catheter were flushed with about 200 mL of isotonic Plasmalyte solution. In all instances, all drains were kept clamped for a minimum of 72 h, except in one patient where a laparotomy had to be performed after 65 h. After administration, the patients were asked to move from side to side in the bed regularly for the first 2 h after installation. For repeated injections, the same in-dwelling peritoneal catheter was used. Drains were removed 3–4 days after administration according to clinical judgment.

The peritoneal distribution of Radspherin particles was examined by gamma-camera imaging and single-photon emission computed tomography/computed tomography (SPECT/CT). The patients were followed closely for diagnostic imaging and safety assessment during the hospital stay and later at prescheduled 3-month intervals until 12 months (1–4 MBq) or 18 months (7 MBq).

3 | Results

All dose levels of Radspherin in this study were well tolerated with no DLTs within 30 days of treatment, no SAEs were considered related to Radspherin in that same time period, and no deaths occurred within 3 months [8].

Twenty-three patients were enrolled (safety population). One was excluded because the final histopathology report 35 days postoperatively classified the tumor as a locally advanced FIGO Stage 3c ovarian/tubal carcinoma instead of the assumed CRC with PM, giving 22 patients in per protocol analyses (Figure 1). This number is used in all figures and tables in this paper.

Clinicopathological characteristics including characteristics after CRS-HIPEC in the 10 patients given 1–4 MBq (Group 1) and in the 12 patients receiving the recommended dose of 7 MBq either as single 7 MBq or split-dose of 3.5 MBq × 2 (Group 2), are presented in Table 1. The median Accordion grade (30-day complication rate) was 2 in both groups, and the median hospital stay was 10.5 versus 13.5 days postoperatively in the two groups.

3.1 | Safety

A total of 253 AEs were registered during the whole study period in the per protocol group ($n = 22$), 75 of them before the injection of Radspherin. The remaining 178 AEs were predominantly of low grade (Grade 1 [115], Grade 2 [53], Grade 3 [8], and Grade 4 [2]), and most were in the dose groups of 1–4 MBq [98] versus 80 in the group with 7 MBq (Table 2). Only seven (four Grade 1 and three Grade 2) AEs were deemed related to Radspherin. With the exception of one event of pyrexia, these events were based on transient laboratory test abnormalities.

Seven of the AEs in Group 1 were classified as SAEs and occurred in five patients, median 2 days (2–332 days) after Radspherin, in contrast to six SAEs in three patients in Group 2,

TABLE 1 | Clinicopathological characteristics in the per protocol cohort ($n = 22$).

	Group 1 (1–4 MBq) $n = 10$	Group 2 (7/3.5 × 2 MBq) $n = 12$
Age, years		
Median	66.5	61.5
Min, Max	44, 78	28, 78
Sex, *n* (%)		
Male	3 (30%)	4 (33%)
Female	7 (70%)	8 (67%)
Stage, *n* (%)		
Stage II	3 (30%)	3 (25%)
Stage III	2 (20%)	3 (25%)
Stage IV	5 (50%)	6 (50%)
Metachr mets	5	6
DFI		
Median (mnt)	13	16.5
Min, Max	6, 25	3, 30
ECOG performance status		
Grade 0	10 (100%)	12 (92%)
Grade 1	0	1 (8%)
Prior chemotherapy, *n* (%)		
Yes	4 (40%)	6 (50%)
No	6 (60%)	6 (50%)
LN+	6 (60%)	8 (67%)
Median	2	1
Min, Max	0, 14	0, 19
PCI		
Median	6	7
Min, Max	4, 17	3, 17
Blood loss (mL)		
Median	300	250
Min, Max	50, 1000	50, 500
Duration of surgery		
Median	403	380
Min, Max	194, 500	266, 508
HIPEC with mitomycin C		
Median (mg)	64	62
Min, Max	59, 70	57, 70
HIPEC in Sweden[a]		
Median (mg)	Comment[a]	Comment[a]
Min, Max	—	—
Hospital stay		
Median	10.5	13.5
Min, Max	7, 37	8, 16

(Continues)

TABLE 1 | (Continued)

	Group 1 (1–4 MBq) $n = 10$	Group 2 (7/3.5 × 2 MBq) $n = 12$
Accordion		
Median	2	2
Min, Max	1, 4	1, 2

Abbreviations: DFI = disease-free interval from surgery for a meachronous primary tumor, Duration of surgery = knife-time, LN+ = number of lymph node metastases, Max = maximum, Min = minimum, n = number of patients in the analysis set, PCI = peritoneal cancer index.
[a]HIPEC in Sweden: Patient 4 MBq Oxaliplatine 620 mg/30 min. Patients repeat injection cohort; Irinotecan 960 mg/90 min or Oxaliplatin 920 mg/30 min or 760 mg/30 min.

TABLE 2 | Adverse events (AEs) in the per protocol cohort ($n = 22$).

	Group 1 (1–4 MBq) $n = 10$	Group 2 (7/3.5 × 2 MBq) $n = 12$
Grade 1	66	49
Grade 2	30	23
Grade 3	2	6
Grade 4	0	2
Total adverse events	98	80

Abbreviations: Grade = CTCAE grade, common terminology criteria for adverse events, MBq = dose of Radspherin, n = number of patients in the analysis set.

occurring a median of 145 days (49–252 days) after Radspherin. All SAEs were evaluated as related to CRS or HIPEC, and unrelated or unlikely related to Radspherin. Four of totally 13 was of Grade 3 and one of Grade 4 (Table 3).

3.2 | Clinical Outcomes

Only one of 22 study patients have died during the study period (OS 96%) (Figure 3a). This was a female given 2 MBq re-operated due to ileus 3 months after CRS-HIPEC and injection of Radspherin. New PM were confirmed and she died 5 months after treatment.

Nine out of 22 patients (41%) have recurred with distant metastasis, mostly in liver or lung (Figure 3b). Median DFS was therefore not reached in the study period of 12/18 months.

Three patients on dose levels 1–4 MBq (Group 1) have recurred in the peritoneum. At 18-month follow-up, none of the 12 patients receiving 7 MBq (Group 2) had evidence of new PM (Figure 3c). Overall, only 25% of patients that received the recommended 7 MBq clinical dose of Radspherin experienced recurrences.

4 | Discussion

CRC with PM carries a dismal prognosis, even after CRS-HIPEC. This particularly relates to the risk of subsequent recurrence of disease, either as distant metastasis, lymph node metastasis, or as PM which often manifests in distinct patterns within the abdominal cavity. For visceral metastases, several effective treatment options exist, however PM have a more aggressive tumor biology [17, 18].

Radspherin generates a short-range alpha-particle radiation field to the surfaces and liquid volumes of the peritoneum and abdominal cavity, thereby delivering lethal doses to remaining micrometastasis in the peritoneal linings and free-floating tumor cells after surgical resection. The aim is to prolong time to any subsequent peritoneal recurrence and thereby potentially improving OS. Such ionizing radiation is effective independently of cancer cell type and may overcome cellular resistance mechanisms for chemotherapy due to its physical nature. According to the limited penetration to 0.1 mm, the risk for damage to healthy tissue is reduced.

The short range of the alpha particles indicate that single cells and micrometastases can be irradiated but larger metastases of a few 100 μm may not be treated effectively by Radspherin. Thus, the effect of Radspherin is dependent of a complete surgical removal of the tumors in the peritoneum.

One interesting feature with the ^{224}Ra-based microparticles is the generation of Radon-220 (Figure 2) which causes some diffusion of radiactive atoms in the vicinity of each particle which causes a "dose smoothening effect" that may be beneficial with this type of product [19].

The low number of AEs and SAEs deemed related to Radspherin supports that the treatment is well tolerated. The low amount of radioactivity detected in blood and urine indicate a low systemic exposure and no precautions related to external exposure from the associated gammas and X-rays seems to be required [20]. There is very low and acceptable level of radiation exposure from the patients to workers at the hospital, and family members [20].

Radspherin has a "mode of action and a benign safety profile that renders this treatment suitable to be studied in combination with, for example, immunotherapy or poly-ADP ribose polymerase (PARP)-inhibitors. In another study, we found a predominately local rather than systemic inflammatory response to CRS-HIPEC, whereas Radspherin had an overall modest impact on the inflammation [21].

PM can originate from several cancer types, and patient numbers are significant. Radspherin provides nonsystemic, receptor-independent, alpha-radiation therapy to the peritoneal linings and liquid volumes of the abdominal cavity, applicable in several different cancer types where PM contributes to a dismal outcome. Hence, Radspherin can be relevant for several cancer forms treated with CRS in the peritoneum. It is also possible that it can be used in other body cavities like the bladder or pleura.

The current data is from a limited number of patients. Accordingly, the results must be evaluated carefully. A further expansion cohort of 24 additional patients given 7 MBq of Radspherin have been completed, and are now in follow-up.

TABLE 3 | Serious adverse events in the per protocol cohort ($n = 22$)[a].

Subject Id	Dose (MBq)	Investigator's AE term	Days between AE start date and IMP adm date	CTCAE grade	Relationship to study drug	Relationship to study/ surgical procedure	Relationship to HIPEC procedure
NO-21-002	1	Leakage rectal anastomosis	2	Grade 2	Unlikely	Unlikely	Probably
NO-21-004	1	Adenocarcinoma	54	Grade 1	Unrelated	Definitely	Unrelated
NO-21-005	2	Abdominal infection	10	Grade 2	Unlikely	Probably	Probably
NO-21-010	4	Anastomotic leakage	9	Grade 3	Unlikely	Definitely	Definitely
NO-21-010	4	Abdominal infection	15	Grade 2	Unlikely	Definitely	Probably
NO-21-010	4	Abdominal infection	41	Grade 2	Unlikely	Definitely	Probably
NO-21-011	4	Depression	332	Grade 1	Unrelated	Unrelated	Unrelated
NO-21-021	7	Bowel obstruction	49	Grade 3	Unrelated	Possibly	Possibly
NO-21-014	7	Vomiting	95	Grade 2	Unrelated	Unrelated	Unrelated
NO-21-021	7	Bowel obstruction	99	Grade 4	Unlikely	Possibly	Possibly
NO-21-021	7	Bowel obstruction	186	Grade 3	Unlikely	Possibly	Possibly
NO-21-016	7	Fever	192	Grade 2	Unrelated	Unrelated	Unrelated
NO-21-021	7	Bowel obstruction	252	Grade 3	Unlikely	Possibly	Possibly

Abbreviations: Grade = CTCAE grade, common terminology criteria for adverse events, MBq = dose of Radspherin.
[a]Complications after the injection of Radspherin.

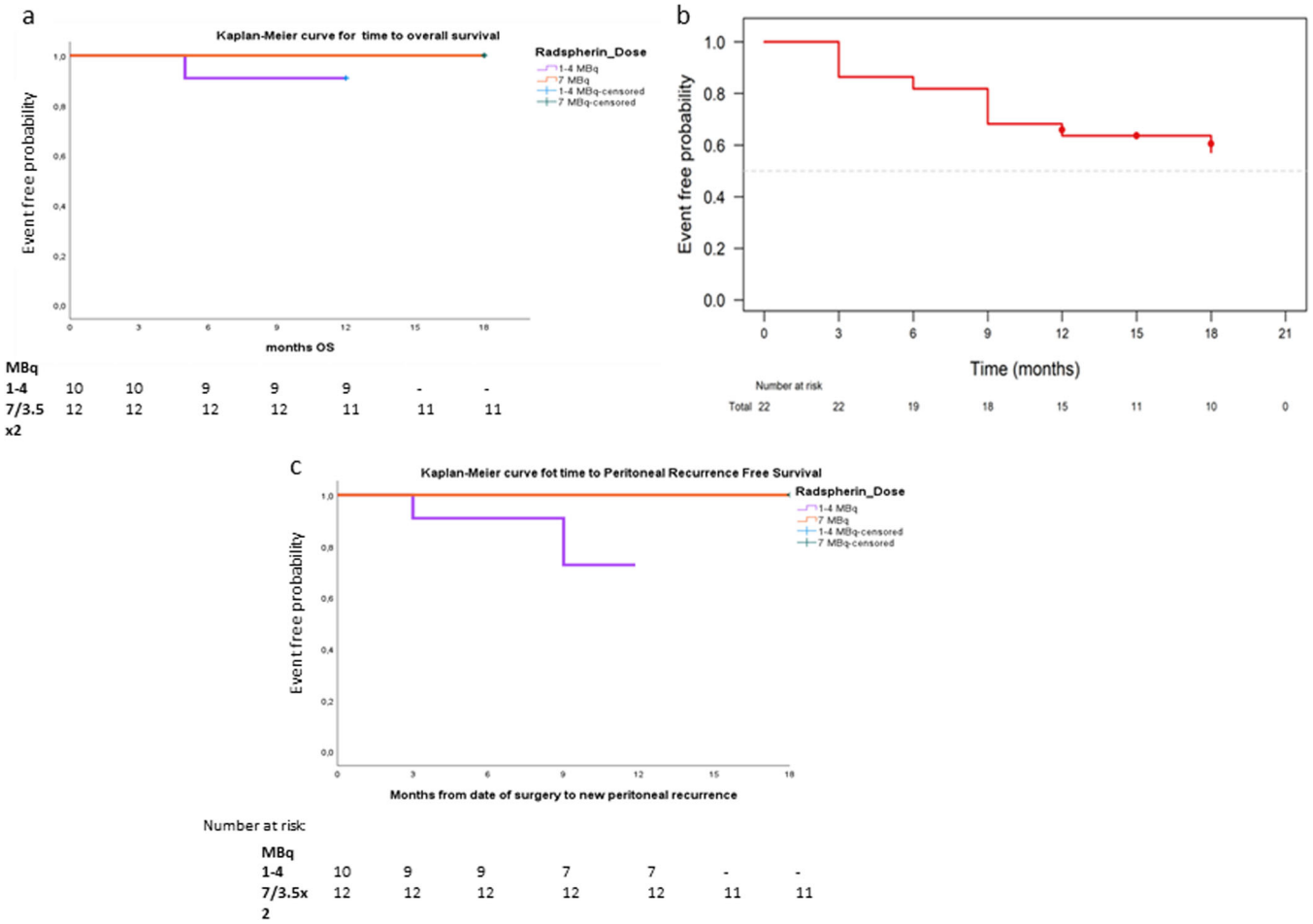

FIGURE 3 | (a–c) Kaplan–Meier curves of the patients given 1–4 MBq ($n = 10$) of 224 Radium versus those given 7 MBq ($n = 12$). (a) Overall survival (OS) in Groups 1 and 2. (b) Disease-free survival (DFS) for all 22 patients. (c) Peritoneal disease-free survival (per-DFS) in Groups 1 and 2.

The study reported here has shown safety data and documented promising signals of efficacy that warrant further exploration of Radspherin as a novel treatment principle in a planned multicenter, randomized controlled trial (IND no 168540/EU CT no 2023-508496-37-00).

5 | Conclusion

Radspherin is a novel alpha-emitting radiopharmaceutical for postoperative administration into the peritoneal cavity, with minimal risk of damage to healthy tissue. To date, safety results indicate that the product is well tolerated. Results of this Phase 1/2a study in patients with PM from CRC show no recurrence of peritoneal metastasis among the 12 patients given 7 MBq after an observation period of 18 months ($n = 22$). The results are encouraging and warrant further clinical development. Results from an additional 24 patients treated with 7 MBq in an expansion cohort are pending.

Author Contributions

S.G.L., R.H.L., and Ø.S.B. participated in conceptualization. A.K.-A., T.J.G., S.G.L., M.E.-R., W.G., R.H.L., and Ø.S.B. participated in study design and drafting the manuscript and revising it critically for important intellectual content. S.G.L., M.E.-R., A.K.-A., T.J.G., W.G., R.H.L., and Ø.S.B. involved in data analysis/interpretation of results. All authors contributed to the article and approved the submitted version.

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Conflicts of Interest

Ø.S.B. is a co-founder, clinical consultant to the board and holds ownership in Oncoinvent ASA. R.H.L. is a co-founder and holds ownership in Oncoinvent ASA. M.E.-R. holds ownership in Oncoinvent ASA. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings are available from the corresponding author.

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