

18-month safety and efficacy after intraperitoneal treatment with ²²⁴Radium-labelled microparticles (Radspherin) after cytoreductive surgery and HIPEC for colorectal peritoneal metastasis



Larsen SG¹, Mariathan AM¹, Sørensen O¹, Spasojevic M¹, Goscinski M¹, Holtermann A¹, Ghanipour L^{2,3}, Cashin P^{2,3}, Bruland Ø^{4,5}, Flatmark K^{1,6}, Aksnes AK⁷, Myren K⁷, Graf W^{2,3}



¹Department of Gastroenterological Surgery, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway, ²Department of Surgical Sciences, Uppsala University, Uppsala, Sweden, ³Department of Surgery, Uppsala Academic Hospital, Uppsala, Sweden, ⁴Faculty of Medicine, Institute for Clinical Medicine, University of Oslo, Oslo, Norway, ⁵Department of Oncology, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway, ⁶Department of Tumor Biology, Institute for Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway, ⁷Oncoinvent AS, Oslo, Norway

Background:

- Peritoneal metastasis (PM) from colorectal cancer carries a high risk of relapse, with median time to recurrence around 12 months after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC)
- Radspherin is a novel treatment principle based on the delivery of short-range and cytotoxic alpha particles emitted during the decay of ²²⁴Ra
- Alpha particles have high linear energy transfer and a radiation range less than 100 µm (3-10 cell diameters), generating highly localized and effective radiation with non-repairable double-strand DNA breaks in affected cells
- Our hypothesis is that Radspherin generates radiation fields almost exclusively to the peritoneal surfaces and liquid volumes of the abdominal cavity, and lethal doses to eradicate remaining micrometastasis in the peritoneal linings and free-floating tumor cells after CRS.

- Thus, the goal is prolonging time to any subsequent peritoneal recurrence, progression free survival (PFS) and potentially with positive impact on overall survival

Methods:

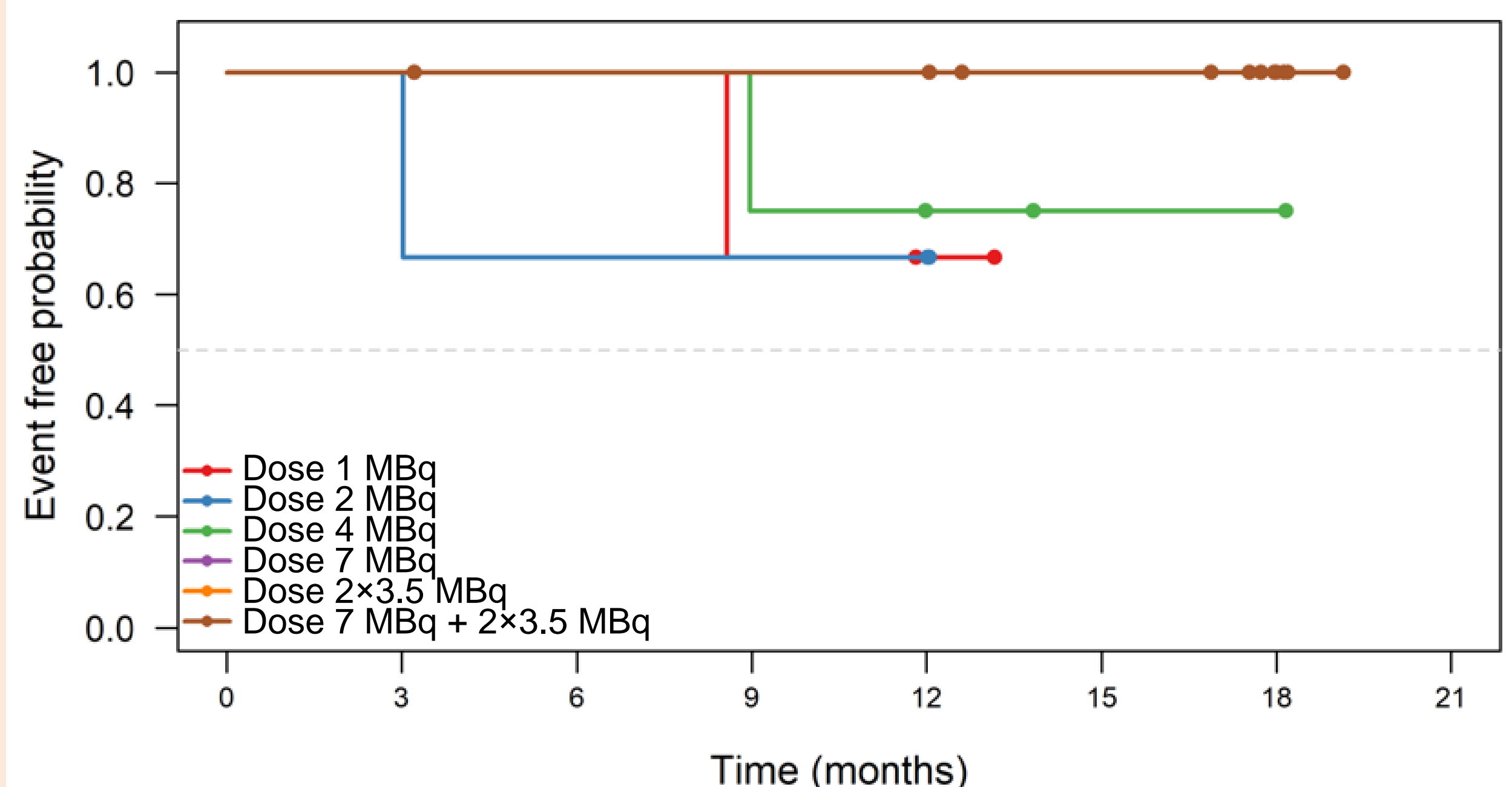
- A phase 1/2a study (NCT03732781) is ongoing to evaluate safety, tolerability and signal of efficacy of Radspherin injected intraperitoneally two days after CRS-HIPEC. After completion of dose escalation (1-2-4-7 MBq), an activity-dose of 7 MBq was recommended, and additional patients were included in an expansion cohort
- Assessment of efficacy (diagnostic CT/MRI) was performed every three months
- Preliminary safety and survival data at 18 months are presented



Radspherin is a novel alpha-emitting radiopharmaceutical specifically designed to deliver high energetic radiation for efficient tumor cell killing intraperitoneally post-surgery

In a study in patients with PM from colorectal cancer treated with Radspherin two days after CRS-HIPEC, none of the patients at recommended dose of 7 MBq had peritoneal recurrences at 18 months. Radspherin was well tolerated with no related SAEs reported and represents a promising novel treatment option warranting further exploration in a randomized study.

Peritoneal recurrence-free survival for the different dose groups



Overall recurrence rates (including non-peritoneal) at 18-month in the different dose groups

Activity dose	1 MBq	2 MBq	4 MBq	7 MBq	2x3.5 MBq	7+2x3.5MBq	Total
n	3	3	4	9	3	12	22
Events (%)	2 (66.7%)	1 (33.3%)	2 (50.0%)	3 (33.3%)	1 (33.3%)	4 (33.3%)	9 (40.9%)

Results:

Baseline Characteristics, safety population (n=23)	
Age (median, range)	64 (28,78)
Gender	Males (7) Females (16)
PCI (median, range)	7 (3-19)
Stage at diagnosis, n (%)	
Stage II	6 (26 %)
Stage III	5 (22 %)
Stage IV	12 (52 %)
Time since initial diagnosis, days (median, range)	198 (21, 803)
Time since diagnosis of peritoneal metastasis (median, range)	50 (15, 168)

- Twenty-three patients were enrolled, one was excluded from the per protocol analysis*
- 12 patients received the recommended dose of 7 MBq

*because of incorrect histopathological diagnosis in final report

- 14 serious adverse events in 8 patients have been reported, none considered related to Radspherin
- At 18-months, none of the 12 patients receiving 7 MBq had peritoneal recurrences, while 4 had recurrences overall (33%)

Term	Events	Patients
Blood creatinine increased	1	1
Intestinal obstruction	4	1
Depression	1	1
Pyrexia	1	1
Vomiting	1	1
Abdominal infection	3	2
Adenocarcinoma	1	1
Anastomotic leak	2	2

- At 18 months 268 adverse events were reported, whereof only 7 (all grade 1-2) evaluated as possibly related to Radspherin

- Across all doses, 9 out of 22 patients (41%) experienced recurrences overall, whereof 3 were peritoneal recurrences in the lower dose levels

Future Directions for Research:

- The study is ongoing and results from additional patients treated with 7 MBq in the expansion cohort are pending
- The results are encouraging and warrant further exploration in a randomized, controlled trial