

# Final safety and efficacy analyses of a phase 1/2a study of intraperitoneal administration of radium-224 labelled microparticles for colorectal peritoneal metastasis following complete CRS-HIPEC

Larsen SG<sup>1</sup>, Sørensen O<sup>1</sup>, Mariathanan AM<sup>1</sup>, Spasojevic M<sup>1</sup>, Ghanipour L<sup>2,3</sup>, Cashin P<sup>2,3</sup>, Bruland Ø<sup>4,5</sup>, Aksnes AK<sup>7</sup>, Myren K<sup>7</sup>, Graf W<sup>2,3</sup>

<sup>1</sup>Department of Surgical Oncology, Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway, <sup>2</sup>Department of Surgical Sciences, Uppsala University, Uppsala, Sweden, <sup>3</sup>Department of Surgery, Uppsala Academic Hospital, Uppsala, Sweden, <sup>4</sup>Faculty of Medicine, Institute for Clinical Medicine, University of Oslo, Oslo, Norway, <sup>5</sup>Department of Oncology, Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway, <sup>6</sup>Oncoinvent AS, Oslo, Norway

## Background:

- Limited treatment options exist for peritoneal metastases from colorectal cancer (PMCRC), which remain a strong driver for poor prognosis. These patients carry a high risk of relapse despite a comprehensive treatment comprising cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), with median time to recurrence around 12 months after treatment.
- Radspherin is a novel alpha-emitting therapy, using the radionuclide radium-224 attached to biodegradable calcium carbonate microparticles.
- Intraperitoneal injection shortly after surgery through an indwelling catheter delivers a high dose of alpha-radiation directly to the peritoneum.
- The densely ionizing but short-range alpha particles emitted during radioactive decay of radium-224 generate radiation fields almost exclusively to the peritoneal surfaces and liquid volumes of the abdominal cavity.
- The limited tissue penetration of alpha radiation (<0.1mm) combined with the microparticles' inability to cross the peritoneum minimize normal organ exposure to radiation.
- The aim of treatment is to target free-floating cancer cells and small cancer cell clusters remaining after cytoreductive surgery, offering a promise to prevent subsequent peritoneal disease progression and prolong survival, with minimal risk of damage to normal tissue.

## Results:

- 36 patients (Oslo 26; Uppsala 10) with histologically verified PMCRC were enrolled and treated with CRS-HIPEC followed by 7 MBq of Radspherin.
- At 18 months 241 adverse events were reported, whereof 10 evaluated as possibly related to Radspherin (mainly grade 1-2).
- 25 serious adverse events in 14 patients were reported, of them 18 SAEs deemed to be related to surgery and/or HIPEC. Two of these events were reported as possibly related to Radspherin. Seven SAEs were unrelated to CRS/HIPEC/ Radspherin.
- None of the 6 dosimetry patients received absorbed doses higher than 1 Gy for the dosimetry target organs assessed.
- The highest absorbed doses were found for endosteal bone surface, followed by kidneys, liver and red marrow.
- All patients (100 %) were alive at 18 months after Radspherin treatment.

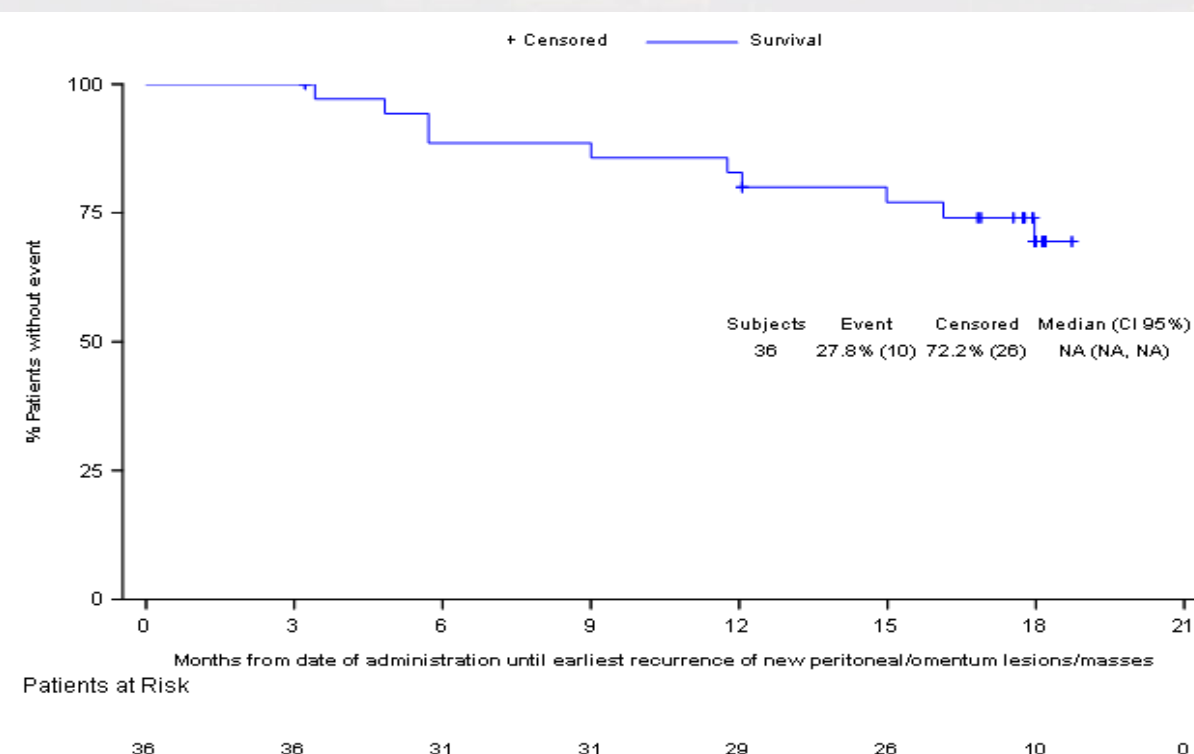
## Methods:

- A phase 1/2a study (EudraCT 2018-002803-33) was performed to assess the safety and efficacy of intraperitoneal Radspherin administered two days after CRS-HIPEC.
- After the phase 1 dose escalation from 1-2-4-7 MBq, 7 MBq was selected as the recommended dose<sup>1,2</sup>.
- These 7 MBq treated patients were followed every 3 months for 18 months or until peritoneal progression. Safety and survival data were collected.

### Characteristics (n=36)

Age, median (min, max)	64 (28, 78)
Gender, n (%)	Males, 16 (44%) Females, 20 (56%)
Stage at primary diagnosis, n (%)	Stage II 8 (22%) Stage III 10 (28%) Stage IV 18 (50%)
Time since primary diagnosis of colorectal cancer, median (min, max)	211 (21, 918)
Synchronous met. disease	50%
Metachronous met. disease	50%
Time since diagnosis of peritoneal metastases, median (min, max)	66 (15, 268)
Any intestinal anastomosis, n (%)	21 (64 %)
PCI, median (min, max)	7.5 (2, 19)
Duration procedure, hours, median (min, max)	5.9 (3, 9)

### Peritoneal recurrence-free survival after Radspherin 7 MBq (Kaplan-Meier)



- 10 out of 36 (27.8%) patients had experienced peritoneal disease recurrence at 18 months, a marked reduction compared to published data for standard of care, where approximately 50% of patients typically see peritoneal recurrence at this stage<sup>3</sup>. Of them, only 2 of 36 patients (5.6 %) experienced peritoneal metastases as the only site of disease recurrence.
- 22 out of 36 patients (61.1%) experienced new metastases of any kind (median disease-free survival 13.5 months).

## Conclusion:

Radspherin is a novel treatment option for patients with peritoneal metastases from colorectal cancer. The study supports the potential of this novel alpha-emitting therapy approach that demonstrates both clinical promise, is well tolerated and safe to use.

<sup>1</sup>Larsen SG, et al. Eighteen-Months Safety and Efficacy Following Intraperitoneal Treatment With (224)Radium-Labeled Microparticles After CRS-HIPEC in Patients With Peritoneal Metastasis From Colorectal Cancer. J Surg Oncol. 2024.

<sup>2</sup>Larsen SG et al. First experience with (224)Radium-labeled microparticles (Radspherin(R)) after CRS-HIPEC for peritoneal metastasis in colorectal cancer (a phase 1 study). Front Med (Lausanne). 2023;10:1070362.

<sup>3</sup>Quenet et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial Lancet Oncol. 2021Feb;22(2):256-266