

15-months safety and efficacy after intraperitoneal treatment with ²²⁴Radium-labelled microparticles (Radspherin) after CRS-HIPEC for peritoneal metastasis from colorectal cancer



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Background:

- Peritoneal metastasis (PM) from colorectal cancer carries a dismal prognosis. Improved survival can be achieved by extensive cytoreductive surgery (CRS), frequently used together with hyperthermic intraperitoneal chemotherapy (HIPEC), with median time to recurrence around 12 months. 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 surgical resection. 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 (EudraCT 2018-002803-33) 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 (pts) were included.
- Assessment of safety and efficacy (diagnostic CT) was performed every three months. Safety and survival data at 15 months are presented

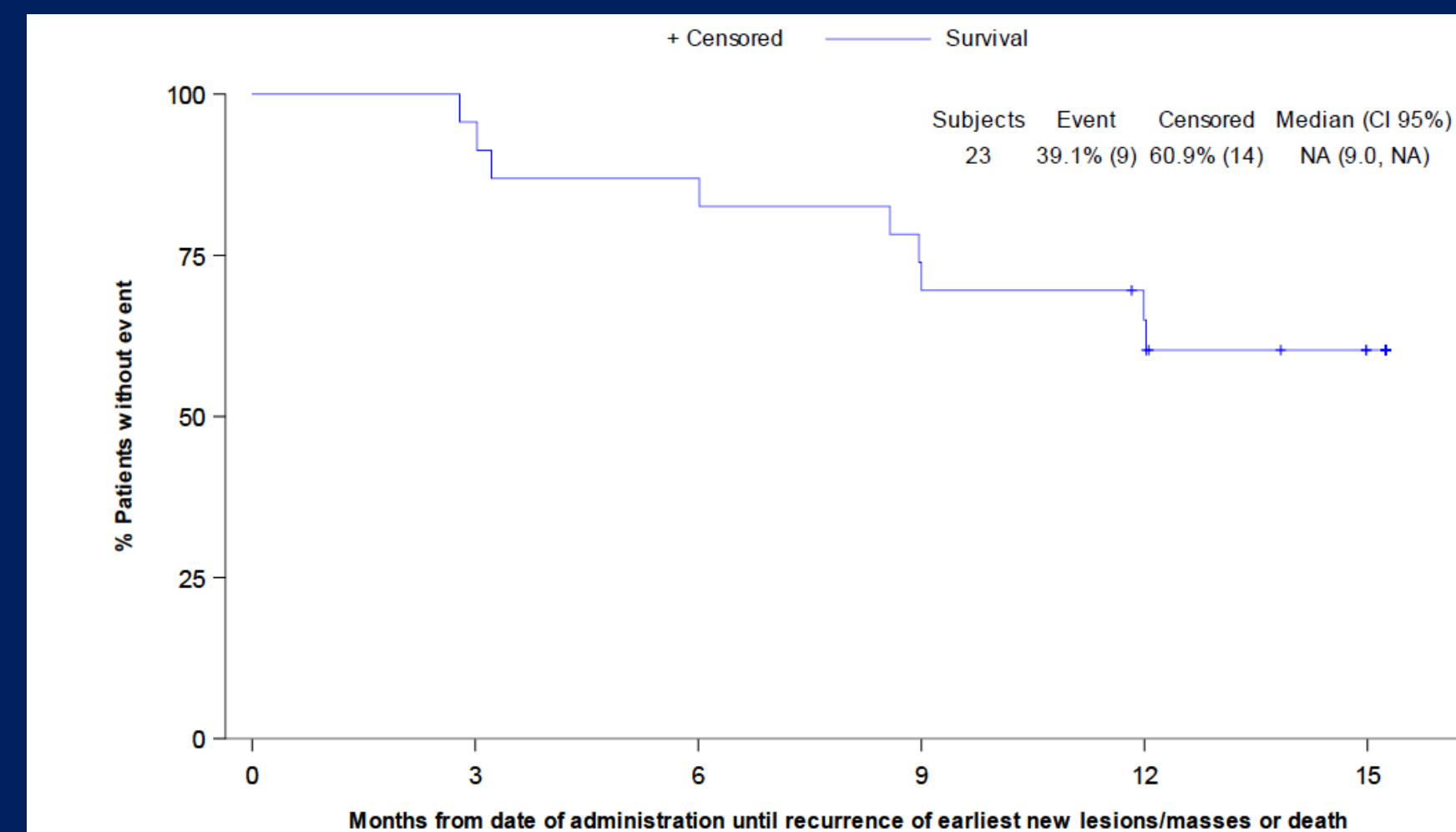


Radspherin is a novel alpha-emitting radiopharmaceutical specifically designed to deliver high energetic radiation for efficient tumor cell killing intraperitoneally post-surgery

In a study in 23 patients with PM from colorectal cancer treated with Radspherin two days after CRS-HIPEC, median PFS had not been reached at 15 months. None of the patients at recommended dose of 7 MBq had peritoneal recurrences. Radspherin was well tolerated with no related SAEs reported and represents a promising novel treatment option warranting further exploration in a randomized study

Activity dose	1 MBq	2 MBq	4 MBq	7 MBq	2x3.5 MBq	7 MBq + 2x3.5 MBq	Total
N	4	3	4	9	3	12	23
Events (%)	2 (50.00 %)	1 (33.33 %)	1 (25.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	4 (17.39 %)

Peritoneal recurrence rates at 15-month in the different dose groups



Kaplan-Meier curve of disease-free survival until month 15 – all pts

Results:

- Twenty-three pts were enrolled across cohorts. Of these 12 pts received the recommended dose of 7MBq; 9 pts as single dose and 3 pts split dose (3,5 MBq x2)

Synchronous PM	12 [stage IV]
Metachronous PM	11 [initial stage II (6), initial stage III (5)]
Disease-free interval (median, range)	15 months [3-39]
Gender	males [7], females [16]
PCI (median, range)	7 [3-19]
Operation time (median, range)	395 minutes [194, 515]
Hospital stay (median, range)	12 days [7-37]

- At 15 months 271 adverse events (AE) were reported, whereof only 7 (all grade 1-2) evaluated as possibly related to Radspherin.
- Fourteen serious adverse events (SAEs) in 8 pts have been reported, none considered related to Radspherin

SAE ≤30 days after IMP adm			SAE ≤6 months after IMP adm			SAE >6 months after IMP adm		
Events	Patients	Grade	Events	Patients	Grade	Events	Patients	Grade
1 Abdominal infection	1	2	2 Intestinal obstruction*	1	3, 4	1 B-Creatinine increased	1	3
1 Abdominal infection	1**	2	1 Vomiting	1	2	2 Intestinal obstruction*	1	3
2 Anastomotic leak	2	2, 3	1 Abdominal infection	1**	2	1 Depression	1	1
			1 Adenocarcinoma	1	1	1 Pyrexia	1	2

SAE-Serious Adverse Event; Grade-CTCAE grade; *4 Intestinal obstruction reported in 1patient; **2 Abdominal infection reported in 1 patient

- At 15 months, 9 out of 23 pts (39 %) had recurred, whereof 4 pts recurred in the peritoneum
- In the recommended dose cohort of 7MBq, 3 out of 12 pts (25 %) had recurred, none of these pts had peritoneal recurrences
- Median PFS was not reached in the two populations

Future Directions for Research:

- The results are encouraging and warrant further exploration of Radspherin as a novel treatment principle in a controlled trial

