



# Safety and efficacy results from a phase 1 study of intraperitoneal alpha-emitting radium-224 labelled microparticles after cytoreductive surgery in patients with peritoneal recurrence of platinum-sensitive epithelial ovarian cancer

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## INTRODUCTION



Alpha-emitters, such as radium-224, emit densely ionizing radiation with high linear energy transfer but low penetration depth. The aim of this Phase 1 study (NCT03732768) was to evaluate safety and tolerability of radium-224 labelled microparticles (Radspherin<sup>®</sup>) and to establish the recommended dose for further clinical development. Results after 24 months follow-up are presented.

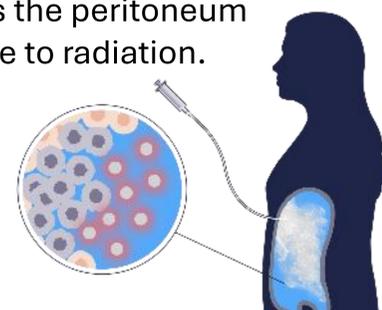
## METHODOLOGY

The study was conducted in patients with platinum-sensitive recurrent ovarian cancer after secondary complete macroscopic cytoreductive surgery. A single intraperitoneal administration of Radspherin was given one to three days postoperatively. Dose escalation (3+3 design) was performed at 1, 2, 4 and 7 MBq activity doses, followed by an expansion cohort on the recommended dose.

## MECHANISM OF ACTION

Radspherin treatment is based on direct delivery of alpha radiation to the peritoneal cavity after surgical resection. This is enabled by the CaCO<sub>3</sub> microparticles that act as depots to retain and distribute the radioactive payload throughout the peritoneal cavity. 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.

- Alpha radiation**
- Positively charged particles with high energy and ultra-short range (stopped by paper or skin)
  - Cause severe, irreparable DNA damage; often a single hit is lethal to a cell, including those having acquired resistance to chemotherapy



## RESULTS

Twenty-one patients were enrolled across the 4 dose levels. Median age was 65 (55-79) years, and median peritoneal cancer index 7 (3-16). All dose levels of Radspherin were well tolerated and no dose limiting toxicities (DLTs), deaths, or discontinuations due to treatment-emergent adverse events (AEs) were reported. 7 MBq was selected as the recommended dose.

A total of 106 AEs were reported, mostly deemed related to the surgical procedure and only 3 events (all grade 1-2) reported as deemed related to Radspherin (Table 2). The most frequently reported AEs were nausea, abdominal pain, constipation, vomiting and urinary tract infections. Only 4 grade 3 events and no grade 4 events were reported. The grade 3 events included two cases of transient ileus, one case of anaemia and one of thrombocytopenia, all reported as deemed unrelated to Radspherin. Six serious AEs were reported (Table 4) of which only one reported as related to Radspherin; a grade 2 procedural complication (disconnect syringe and administration catheter).

A protocol amendment extended the follow-up from 12 to 24 months to allow for assessment of signals of efficacy, as such, most patients on the lower dose levels were only followed for 12 months (data previously published<sup>1</sup>). Ten patients received the 7 MBq recommended dose, and at 24-months follow up only 1 of these 10 had experienced a peritoneal recurrence (Table 3). Two additional patients developed recurrence in extra-abdominal lymph nodes.

Characteristic	1 MBq (N=3)	2 MBq (N=3)	4 MBq (N=4)	7 MBq (N=11)	Total (N=21)
Age, median (range)	62 (56, 63)	68 (62, 74)	72 (66, 77)	59 (55, 79)	65 (55, 79)
FIGO stage, n (%)					
Stage I	0	1 (33%)	2 (50%)	0	3 (14%)
Stage II	1 (33%)	0	0	1 (9%)	2 (10%)
Stage III	2 (67%)	2 (67%)	1 (25%)	7 (64%)	12 (57%)
Stage IV	0	0	1 (25%)	3 (27%)	4 (19%)
Months since initial diagnosis, median (range)	25 (15, 28)	75 (25, 91)	36 (5, 57)	36 (18, 115)	28 (5, 115)
PCI, median (range)	7 (6, 10)	6 (3, 7)	8 (6-16)	7 (3-14)	7 (3, 16)

n=number of patients, PCI (peritoneal cancer index)

Table 1 Baseline characteristics, safety set

Events Preferred term	1-4 MBq (n=10)		7MBq (n=11)	
	Events	Grade	Events	Grade
Abdominal discomfort	0	-	1	1
Abdominal pain	0	-	1	1
Procedural complication	0	-	1	2

Table 2 Related treatment emergent adverse events by preferred term (safety set)

Activity dose	Recurrences at 24 months	
	Peritoneal recurrence	Overall recurrence (including peritoneal)
7 MB, n=10*	1 (10%)	3 (30%)

Table 3 Recurrence rates for patients receiving the recommended activity dose of 7 MBq \*One patient was underdosed (procedural complication) and excluded from the efficacy analysis

Dose	Event term	Start day	Grade	Relationship to Radspherin	Relationship to surgery
1-4 MBq	Compression fracture	295	2	Unrelated	Unrelated
	Ileus paralytic	9	3	Unrelated	Probably
	Intestinal obstruction	247	2	Unrelated	Unrelated
	Ileus	7	2	Unrelated	Probably
7 MBq	Ileus	185	3	Unlikely	Possibly
	Procedural complication	1	2	Possibly	Unrelated

Table 4 Treatment emergent serious adverse events

**CONCLUSIONS** All dose levels were well tolerated, with no DLTs observed. The highest administered activity of 7 MBq was selected as the recommended dose. Only one grade 2 event (procedural complication) was deemed related to Radspherin. At 24-months, only 1 of the 10 patients treated with the recommended dose experienced peritoneal recurrence, encouraging for the ongoing randomized Phase 2 study (NCT06504147) at interval debulking surgery during first-line chemotherapy in ovarian cancer.