First experience with 224Radium-labelled microparticles (Radspherin®) after CRS-HIPEC for peritoneal metastasis in colorectal cancer (a Phase 1 study)

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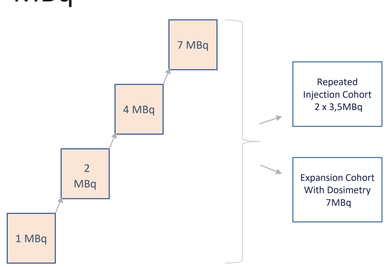
Background:

- Peritoneal metastasis (PM) from colorectal cancer carries a dismal prognosis. Improved survival can be achieved by combining extensive cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC)
- However, median time to recurrence is short (11-12 months) and there is a need for novel therapies to prolong disease-free interval

- Radspherin® consists of α-emitting radium-224 (^{224}Ra), half-life 3.6 days, adsorbed to a suspension of biodegradable calcium carbonate microparticles, designed to give short-range radiation to the serosal peritoneal surface, aiming to kill remaining free cancer cells and small tumor cell clusters

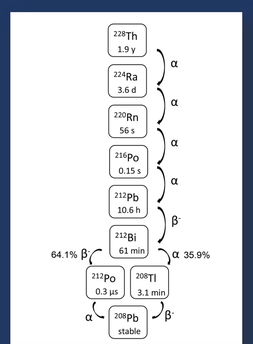
Methods:

- First-in-man phase 1 study (EudraCT 2018-002803-33) sponsored by Oncoinvent AS, conducted at two specialized CRS-HIPEC centers
- Radspherin® injected intraperitoneally two days after CRS-HIPEC
- Dose escalation to define the maximum tolerated dose of the dose levels 1, 2, 4 and 7 MBq
- Biodistribution assessment by planar gamma-camera, as well as SPECT/CT imaging
- Results from the safety interim analysis after the dose-limiting toxicity (DLT) period are presented

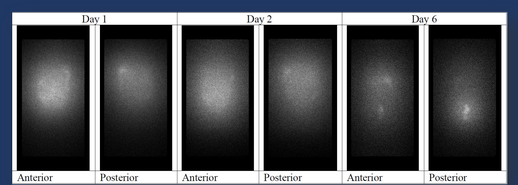


Radspherin® is a novel alpha-emitting radiopharmaceutical specifically designed to deliver high energetic radiation for efficient tumor cell killing when injected intraperitoneally after complete surgical resection, while minimizing risk of harming sensitive organs.

Preliminary safety result of a first-in-man study in patients with colorectal cancer with peritoneal metastasis showed that all dose levels were well tolerated without any dose limiting toxicity. No deaths occurred and no serious adverse events (SAEs) were considered related to Radspherin®. Post-administration gamma-camera imaging showed good peritoneal distribution of the radiolabeled microparticles.



Decay chain of ^{224}Ra from the parent ^{228}Th to stable ^{208}Pb



The biodistribution of 224Ra labelled micro particles in the peritoneal cavity for patient NO-21-020 was evenly distributed in the abdominal cavity with a decrease in activity over time both in anterior and posterior images.
In this subject an area with slightly higher activity was observed in the left upper region. No areas with low levels of activity (cold spots) were observed.
Outside cavity uptake was observed in the large intestine . No activity registered in the kidney or liver.

Results:

- 23 patients enrolled; median age 64 years (28-78)

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]

- All dose levels of Radspherin® were well tolerated, 7MBq selected as recommended dose
- No DLTs, deaths, SAEs considered related to Radspherin®, or discontinuations due to treatment emergent adverse events (TEAEs) were observed
- 185 TEAE were recorded, most of low grade and considered related to CRS and/or HIPEC
- Seven patients had low grade TEAEs considered related to Radspherin® and CRS-HIPEC
- 11 serious TEAEs were reported for 8 patients, unrelated to Radspherin®
- Six accordion ≥3 grade events were reported, assessed as related to CRS-HIPEC and unrelated to Radspherin®:
  - anastomotic leaks (2)
  - Intraabdominal abscess (1)
  - drain complications (2)
  - missed lesion (1)
- Post-administration imaging showed even distribution of Radspherin® in the peritoneal cavity

Future Directions for Research:

- Long-term safety, dosimetry and signal of efficacy will be reported after 18 months follow-up