Preclinical Evaluation of a Novel Alpha-Particle Emitting Therapeutic Agent for Intraperitoneal Therapy of Peritoneal Metastases

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Objectives
We have developed a composition of microparticles and an α-emitting radionuclide, specifically designed for local treatment of peritoneal carcinomatosis. The inorganic microparticles act as carriers for the α-emitter radium-224 (224Ra). This novel α-radiation therapy has a range in tissue of less than 100 μm and is designed to confine the radiation exposure to the intra-peritoneal (IP) cavity, including peritoneal surfaces and liquid volumes. The therapeutic efficacy and safety of the 224Ra-microparticles in mice with human IP xenografts are presented.

Methods
CaCO₃ microparticles with median diameters of 17-21 μm were radiolabeled by precipitation of 224Ra on the particle surface. The 224Ra-microparticles were evaluated in immunodeficient athymic nude mice inoculated IP with human ovarian cancer cells SKOV-3luc or ES-2. Both cell lines represent epithelial adenocarcinoma. SKOV-3luc has a solid tumor growth pattern, whereas inoculation with the ES-2 cell line leads to aggressive development of ascites and at later stages invasive tumor growth. Different activity levels of 224Ra-microparticles were administered IP as a suspension, with a volume between 250-400 μl per mouse. Tumor growth, survival, and blood parameters were assessed. A maximum of 100 μl blood was collected from the vena saphena lateralis in EDTA tubes at 3 time points during the ES-2 study for hematology analyses of platelets, white and red blood cells. Blood was collected from heart puncture in sedated animals prior to euthanasia for hematology analyses in the SKOV-3luc study and for clinical chemistry in the ES-2 study (urea, aspartate and alanine aminotransferases and alkaline phosphatase).

Results
Intraperitoneal treatment with 224Ra-microparticles resulted in inhibition of tumor growth in mice inoculated with SKOV-3luc (Fig. 1). A significant reduction in IP tumor weight was obtained in all treatment groups. Further, treatment with 224Ra-microparticles in the ES-2 xenograft model with aggressive development of ascites gave a survival benefit (Fig. 2). A wide dose range of 224Ra-microparticles was assessed, and the results showed that all doses tested resulted in at least a doubling of median survival compared to the control group. Analyses of blood samples of mice treated with 224Ra-microparticles showed no radiation related effects on neither hematologynor clinical chemistry parameters. Selected hematology data from mice treated with up to 1000 kBq/kg of activity are shown in Fig. 3. An increased white blood cell count in control animals during disease progression was observed in the ES-2 (day 13 Fig. 3) and SKOV-3luc model (not-shown), and in the group given the lowest dose in the ES-2 study (day 26 Fig. 3). No changes related to treatment were observed.

Conclusions
The presented preclinical data show that only a few kilobecquerels per mouse of 224Ra-microparticles were needed to yield therapeutic effects. The treatment was well-tolerated up to doses of 1000 kBq/kg. Intraperitoneal α-therapy with 224Ra-microparticles demonstrates a significant potential for treatment of residual microscopic IP disease.

References
2. Westrøm et al., in prep. Therapeutic Effect of α-Emitting 224Ra-labeled Calcium Carbonate Microparticles in Mice with Intraperitoneal Ovarian Cancer.