

# New Image-guided Alpha Particle Therapy for NETs in Children and Adults

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**Background:** Neuroendocrine tumors (NETs) are a rare form of cancer whose incidence is increasing. In the development of effective therapy, high expression of somatostatin receptor subtype 2 (SSTR2) has been identified as a potential target for drug delivery, including peptide receptor radionuclide therapy using DOTA<sup>0</sup>-Tyr<sup>3</sup>-octreotide (DOTATOC). While beta particle therapies using <sup>90</sup>Y/<sup>177</sup>Lu have been extensively examined, the potential advantages of alpha particle therapy have been relatively unexplored. Within this context, we are developing a new image-guided <sup>203</sup>Pb(imaging)/<sup>212</sup>Pb(therapy) approach that we anticipate will impart a higher RBE (relative biological effectiveness) via targeted alpha particle deposition in NETs and improve outcomes compared to current beta particle therapies.

**Methods:** Pancreatic carcinoid (BON-1) cells were implanted subcutaneously in nude mice and a bio-distribution study was conducted by injecting 1 μCi of <sup>203</sup>Pb/<sup>212</sup>Pb-DOTATOC via tail vein. Mice were euthanized at 1h, 3h, and 24h post-injection (n=3); tissues of interest were harvested and radioactivity measured. These data were used to inform a SPECT/CT imaging study (180 μCi of <sup>203</sup>Pb-DOTATOC was injected via tail vein) at 1 h post injection. A pilot therapeutic study was then conducted in BON-1 tumor bearing mice (3 groups: control, single dose, and 3 fractionated doses; total dose ~120μCi of <sup>212</sup>Pb-DOTATOC). Ongoing survival studies reveal a significant survival benefit and tumor control in <sup>212</sup>Pb-DOTATOC treated NET tumor bearing mice relative to untreated mice.

**Results:** Excellent tumor contrast was observed in the first <sup>203</sup>Pb-DOTATOC SPECT/CT images of human NETs obtained in these pilot studies. Biodistribution and imaging studies informed <sup>212</sup>Pb-DOTATOC therapy in which significant survival improvement and reduction in tumor growth was observed in human NET bearing mice.

**Conclusion:** A <sup>203</sup>Pb/<sup>212</sup>Pb theranostic combination is a promising alternative for image-guided radionuclide therapy for NETs and other SSTR2 expressing tumors.