ACTINIUM-225 AND BISMUTH-213 ALPHA PARTICLE IMMUNOTHERAPY OF CANCER

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Nuclides with appropriate half-lives and emission characteristics that would be potent enough to kill neoplastic cells in the small quantities that reach targets in vivo, include the high linear energy transfer (LET) alpha emitters such as Actinium-225 and Bi-213. We developed methods for the attachment of radiometals via bifunctional chelates to monoclonal antibodies (mAb) without loss of immunoreactivity. We developed alpha-emitting Bi-213 lintuzumab constructs, characterized and qualified them in preclinical models, and took them into human clinical trials in patients with AML. Safety, anti-leukemic activity, and complete responses (CR's) have been demonstrated through phase 2 trilas. Bi-213 is produced in a portable small generator device based on Ac-225 in the hospital nuclear medicine lab. The isotope is then purified, attached to the antibody, and the product is qualified and processed. Despite this success, the major obstacle to the widespread use of these drugs remains the short ^{213}Bi half-life (46 minutes), which poses a large logistical hurdle before injection and limits its delivery to only the most accessible cancer cells after injection (Fig 1.)

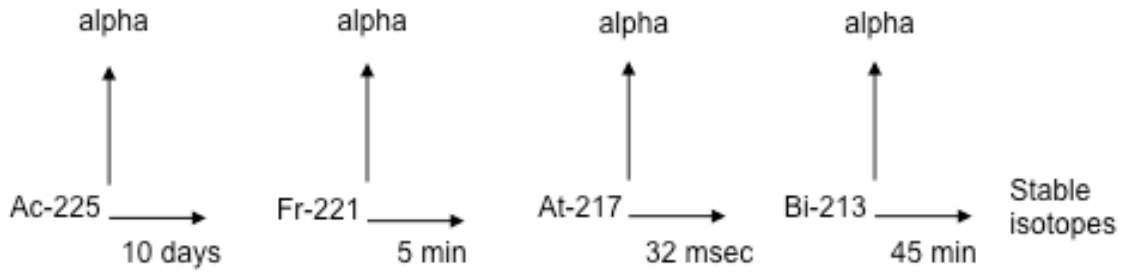

FIG. 1. Simplified Ac-225 generator to Bi-213 decay scheme yielding four net alphas

Our solution to these constraints for Bi-213 was to deliver the Ac-225 atomic generator itself to the target cell, allowing production of the atoms in vivo that will yield potent alpha emissions at or in the cancer cell. For this process to be successful pharmacologically, the device must possess molecular dimensions. At its ultimate reduction, the device therefore consists of a single generator atom attached to the delivery vehicle. Actinium-225 has a 10.0-day half-life and decays via alpha emission through three atoms, each of which also emits an alpha particle. We developed methods that use bifunctional versions of the chelating moiety DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) to stably bind 225Ac to the delivery vehicles, and have described the synthesis, purification, and analyses of the resulting constructs. The "in vivo generators" or "atomic nanogenerators" were successfully tested in vitro in several systems, showing 1000-fold increases in potency (on a mCi basis) thereby making this a cost-effective approach, and were active in several model systems in mice (disseminated leukemia, colon cancer, prostate cancer, ovarian cancer, neuroblastoma, lung cancer, glioblastoma). Administration IV, IT, and IP were possible. Targeting of neovasculature of tumors was also effective. Preclinical methods to use the Ac-225 nanogenerator as part of a "2-step" pretargeting approach to therapy have also been demonstrated.

Based on the preclinical body of work, phase 1 trials in humans with AML were begun, showing, safety, anti-leukemia activity, and logistical ease of production and administration, in which drug could be made at a central site (Houston, Tx) and shipped to multiple sites throughout the USA. The cGMP manufacturing has been FDA approved for multicenter use. Theoretical toxicities to organs, such as kidney, related to the daughter products, were not seen.

The technology has been licensed from Sloan-Kettering Institute to Actinium Pharmaceuticals, which is sponsoring current trials and drug production. While current supplies of Ac-225 are available from U-233/Thorium-229 supplies in the USA, EU, and Russia, a scalable cyclotron-based method of production has been developed by Actinium in Munich and also by the ITU.