

## Current Landscape and Clinical Progress of Targeted Alpha Radioimmunotherapy

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Theranostics is an expanding area of cancer research that describes the use of radiotracers to first diagnose and then treat cancer. By coupling a radioisotope to an agent that selectively targets malignant cells, one can distribute focused radiation to disease sites. There are a variety of different radiopharmaceutical vectors that have been utilized in this way, such as peptides, small molecules and antibodies. Because antibodies bind to highly specific antigens, radioimmunotherapy (RIT) allows radioisotopes to emit energy, inducing DNA breaks and destroying tumor cells, in a specific, systemic manner that other radiation strategies cannot do. Beta ( $\beta$ )-emitting isotopes (e.g., <sup>131</sup>I, <sup>90</sup>Y) have been more commonly coupled in RIT, but the use of alpha ( $\alpha$ )-emitters (e.g., <sup>225</sup>Ac, <sup>212</sup>Pb), for RIT ( $\alpha$ -RIT) has rising popularity due to their shorter tissue range and higher linear energy transfer. These characteristics decrease off-target effects in neighboring tissues and increase tumor cell destruction, respectively. There are a variety of  $\alpha$ -RIT agents currently in clinical development to treat hematologic malignancies, metastatic castration-resistant prostate cancer, and other difficult-to-treat solid tumors. This literature review highlights these agents and shows there are several challenges to  $\alpha$ -RIT. The production of daughter isotopes from  $\alpha$  decay makes dosimetric assessments difficult and could cause off target toxicities. Additionally, whole antibodies tend to accumulate in liver tissue and have long biological clearance times, which may cause excess radiation to the blood, marrow and liver. Strategies to widen the therapeutic indices of these agents have been investigated such as pretargeting, use of antibody fragments, chelator optimization and combination therapies. More studies to further evaluate  $\alpha$ -RIT are critical to optimize the use of this technology. There are many clinical trials underway, and we eagerly await their results.