JAMA Oncology | Review

Targeted Alpha Therapy, an Emerging Class of Cancer Agents
A Review

Targeted Alpha Therapy Working Group

IMPORTANCE Targeted alpha therapy attempts to deliver systemic radiation selectively to cancer cells while minimizing systemic toxic effects and may lead to additional treatment options for many cancer types.

OBSERVATIONS Theoretically, the high-energy emission of short-range alpha particles causes complex double-stranded DNA breaks, eliciting cell death. No known resistance mechanism to alpha particles has been reported or scientifically established. The short-range emission of alpha particle radiation confines its cytotoxic effect to cancerous lesions and the surrounding tumor microenvironment while limiting toxic effects to noncancerous tissues. The high level of radiobiological effectiveness of alpha particles, in comparison with beta emissions, requires fewer particle tracks to induce cell death. Clinically effective alpha particle–emitting isotopes for cancer therapy should have a short half-life, which will limit long-term radiation exposure and allow for the production, preparation, and administration of these isotopes for clinical use and application. Radium 223 dichloride is the first-in-class, commercially available targeted alpha therapy approved for the treatment of patients with metastatic castration-resistant prostate cancer with bone metastases. Given the established overall survival benefit conferred by radium 223 for patients with metastatic castration-resistant prostate cancer, several other targeted alpha therapies are being investigated in clinical trials across many tumor types.

CONCLUSIONS AND RELEVANCE Targeted alpha therapy represents an emerging treatment approach and provides for the possibility to bypass mechanisms of acquired resistance in selected tumors. In addition, developing novel radionuclide conjugation strategies may overcome targeting limitations. So far, the clinical success of radium 223 has demonstrated the proof of concept for targeted alpha therapy, and future studies may lead to additional treatment options for many cancer types.

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Supplemental content

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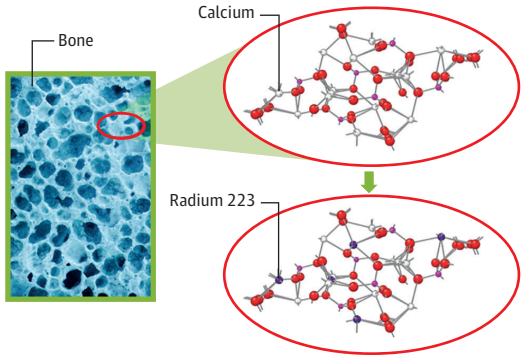
The Targeted Alpha Therapy Working Group defines *targeted alpha therapy* (TαT) as an agent that delivers systemic radiation selectively to cancer cells and the tumor microenvironment to control cancer while minimizing toxic effects. Targeted alpha therapy can be delineated into 2 primary categories of payload delivery. The first approach uses the inherent molecular properties of the radionuclide agent, whereby radionuclides naturally accumulate in cancerous tissue. For instance, the alpha particle–emitter radium 223 is a calcium-mimetic isotope that is incorporated into sites of increased bone turnover and osteoblastic activity (**Figure 1**A).[1-5] The second approach conjugates alpha particle–emitting radionuclides to monoclonal antibodies (mAbs) (Figure 1B),[1,2] peptides, or small molecules to target tumor-associated antigens (Figure 1C),[1,2] allowing for the possibility of targeting a wide range of tumor types.[1,6] The emission of short-range alpha particles causes complex double-stranded DNA breaks through high linear-energy transfer (LET), triggering cell death and, importantly, having no known resistance mechanism.[5,7,8] Delivering short-range, high-energy radiation in a targeted manner may allow for the treatment of localized or metastatic tumors[9] with minimal toxic effects to surrounding noncancerous tissue. This review aims to define the TαT concept and review the rationale and considerations for its development and implementation as a viable treatment strategy in oncology.

Rationale for TαT

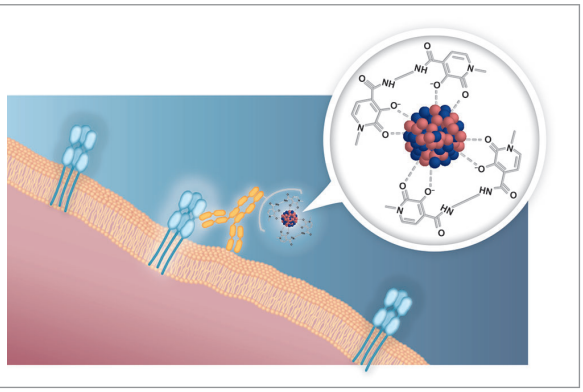
Radionuclides may be arbitrarily classified by their emission of alpha, beta, and Auger particles.[10] The distinct characteristics that determine the therapeutic effectiveness of a specific radionuclide include their potential range when emitted, their effective travel distance in tissue, the magnitude of energy emitted, and their relative biological effectiveness.[11] Particles emitted by radionuclide decay can be categorized as low-LET or high-LET radiation, which is a measure of the energy released per unit distance.[9,12,13] High-LET alpha particles are more cytotoxic than are low-LET beta particles.[9,12] Beta

Figure 1. Mechanisms of Targeted Alpha Therapy (TαT)

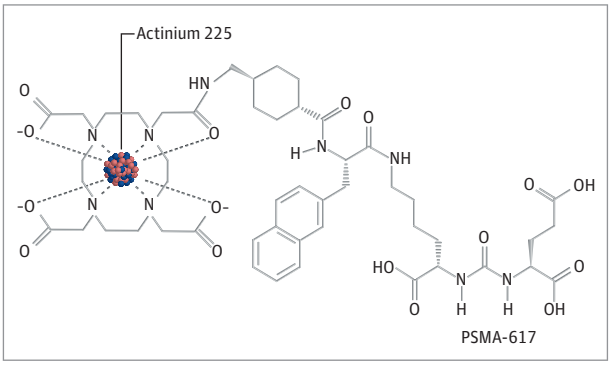
A Molecular-mediated TαT



B mAb-mediated TαT



C Small-molecule-mediated TαT



A, Molecular-mediated TαT is reliant on the inherent chemical properties of the alpha particle–emitting isotope to incorporate into target tissues. The example shown is radium 223, an alpha particle emitter and a calcium-mimetic isotope. It can be incorporated into sites of increased bone turnover and osteoblastic activity. B, Monoclonal antibody (mAb)–mediated TαT. Alpha particle–emitting radionuclides are conjugated to mAbs to facilitate delivery of the radionuclide to targeted tumor-associated antigen epitopes on tumor cells. The example shown is the *N*-hydroxysuccinimide-activated 3,2-hydoxypyridinone chelator coupled to lysine residues of the desired antibody, which is radiolabeled with thorium 227. C, Small-molecule–mediated TαT. The example shown is actinium 225 conjugated to DOTA [$(CH_2CH_2NCH_2CO_2H)_4$]–based prostate-specific membrane antigen 617 (PSMA-617),[1] which targets and delivers actinium 225 to PSMA-expressing prostate cancer cells. Adapted from chapter 4 in *Biomedical Engineering–Frontiers and Challenges* under CC-BY-NC-SA 3.0 license.[2]

particles are emitted electrons (charge of −1) that have a low LET (0.2 keV/μm) and relatively long (1-10 mm) range in tissue.[12-14] Alpha particles consist of a helium nucleus with a charge of +2 and have significantly greater mass than do beta particles.[11,12,14] Alpha particles have an LET range of 50 to 230 keV/μm[7,12-14] and a travel distance in tissue of typically 50 to 100 μm (**Figure 2**).[12,14] The comparatively reduced "crossfire effect" of alpha particle radiation results in reduced toxic effects to surrounding healthy tissue.[14]

Beta particles produce sparse ionization events and individual DNA lesions, which are mostly repairable single-stranded and double-stranded DNA breaks that have a low probability of being lethal.[7,14] Conversely, a single alpha particle can induce a greater number of ionization events and clusters of double-stranded DNA breaks, which often result in cell-cycle arrest followed by mitotic cell death, apoptosis, or necrosis.[7,9,14] Clusters of DNA lesions are far more difficult to repair than the breaks induced by the emission of beta particles.[15] Moreover, alpha particle–induced cell damage has been shown to induce immunogenic cell death, and targeted alpha therapies could potentially augment the efficacy of immuno-oncology or other anticancer agents when used in combination. Alpha particle–induced cell damage can generate antigen-specific T-cell responses, and the immunostimulatory environment created by TαT can be exploited to achieve a robust and effective antitumor response.[16] In addition, alpha particle irradiation can induce a number of off-target effects, including the generation of radical oxygen species, the induction of the DNA damage response, and the repair and activation of stress signals relating to forms of radiation injury and apoptosis. In vivo evidence also indicates that the off-target radiation effects resulting in tumor regression are observed at sites distant from the site of irradiation, suggesting a systemic abscopal effect.[17]

Developments in the targeted delivery of radionuclides and in radionuclide conjugation chemistry, and the increased availability of alpha particle emitters appropriate for clinical use, have led to clinical trials evaluating the safety and efficacy of TαTs across multiple indications.[7,14] The potential of alpha particle emitters to treat cancer has been recognized for more than a century.[7] The first clinical trial of a TαT in 1997 used the radionuclide bismuth 213 conjugated to the leukemia antibody HuM195.[7]

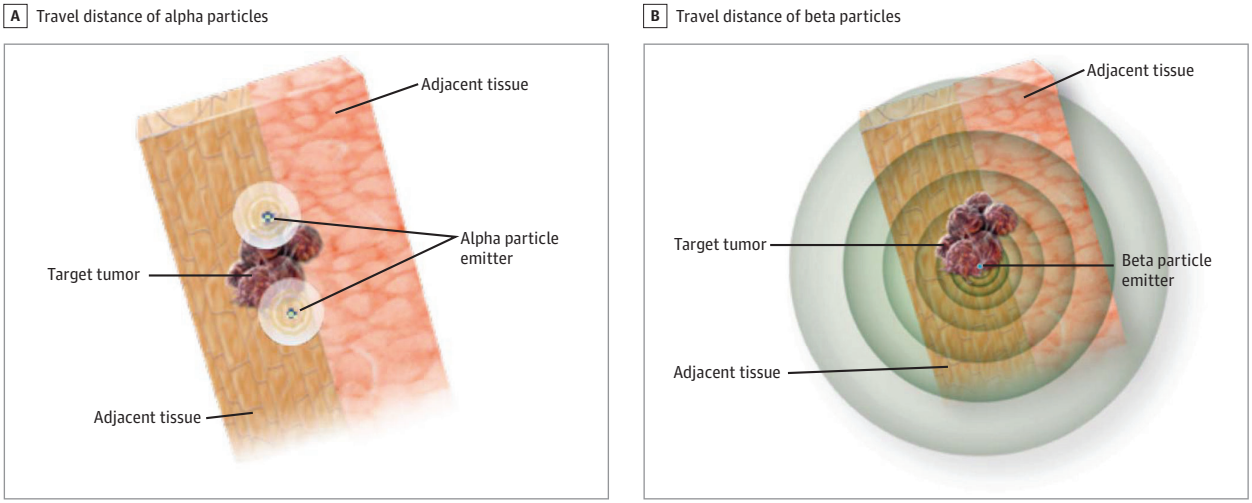
Considerations for Isotope and Conjugation Choices for TαT

Alpha Particle–Emitting Isotopes

More than 100 radionuclides emit alpha particles as they undergo radioactive decay; however, the number of isotopes with the appropriate properties for consideration of a TαT suitable for clinical use in cancer treatment is limited.[18,19] Alpha particle–emitting isotopes appropriate for cancer therapy must have a short half-life to limit the long-term toxic effects of radiation but must still have a long enough half-life for practical production, preparation, and administration.

Another important consideration for TαT is the decay pattern of alpha particle–emitting isotopes. The daughter isotopes (the nuclide remaining after radioactive decay) should preferably decay sufficiently rapidly to ensure that all subsequent radiation is restricted to the targeted tumor and to allow for rapid clearance to avoid off-target toxic effects. Furthermore, the association between the

Figure 2. Relative Alpha Particle vs Beta Particle Emission Range in Tissue



kinetics of daughter isotope decay and the kinetics of tumor growth must be considered when selecting an isotope for potential therapy. Aggressive tumor types may benefit from the use of an isotope with a short half-life to maximize dose rate and intensity. Treatment of indolent tumor types, in contrast, may benefit from an alpha-emitting radionuclide with a longer half-life, allowing for sustained alpha particle bombardment of the targeted tumor and tumor microenvironment.

Targeted Delivery of Alpha Particle–Emitting Isotopes

Therapeutic agents that use alpha particle–emitting radionuclides must use their inherent tissue-targeting properties or require the stable conjugation of the radionuclide to a targeting moiety to facilitate tumor recognition. The stability of TαTs in vivo is dependent on the chemical nature of the parent radionuclide. For instance, the chemical properties of the halide astatine 211 facilitate direct radiolabeling of mAbs.[12,18] Other alpha-emitting radionuclides possess metallic properties and require chelation chemistry to label antibodies, peptides, and small molecules.[12,14,20-33] However, some radionuclides are not able to stably interact with chelating agents. For example, radium 223 chelation and conjugation to biomolecules have been largely unsuccessful.[34] If the alpha particle emission energy or recoil energy of the daughter radionuclide exceeds the binding energy of the chelating agent, the daughter radionuclide may not be retained at the target site, leading to off-target toxic effects.[34]

Monoclonal Antibody, Peptide, and Small-Molecule Conjugates

The primary advantage of using tumor-specific mAbs in TαT is the specificity and affinity for tumor-associated antigen epitopes on tumor cells. Full-length mAbs contain 2 identical fragment antigen–binding regions and a fragment crystallizable or constant region.[35] Several potential disadvantages have been identified with the therapeutic use of full-length mAbs, which may affect the use of full-length mAb–mediated TαT. The high molecular weight of mAbs results in a long serum half-life, and the nonspecific uptake of the antibody via the fragment crystallizable region in cells of the innate and adaptive immune system may lead to nontargeted irradiation.[14,35] Nonspecific mAb-mediated TαT interaction with myeloid and hepatic sinusoidal cells can result in myelosuppression and liver toxic effects.[14] Antibody engineering efforts have been made to develop antibody fragments and mAb derivatives that are smaller in size and lack a fragment crystallizable region to shorten serum half-life and limit off-target uptake without sacrificing specificity and affinity.[35] Smaller engineered mAb derivatives clear the circulation more rapidly and penetrate target tumors more effectively, providing increasingly favorable tumor to background ratios.[14,35]

In addition to full-length mAb and engineered mAb fragment use, ligands, synthetic protein scaffolds, and substrate analogues can also be used as TαT targeting agents. Examples include the conjugation of thorium 227 to a full-length mesothelin antibody to target mesothelin-expressing cancer cells and the conjugation of actinium 225 to the small-molecule, prostate-specific membrane antigen 617 to target prostate cancer cells.[1,36] The use of these targeting moieties results in shorter serum half-lives and rapid targeted uptake into tumors.[14,35] However, the use of affibodies and nanobodies can result in increased risk of off-target toxic effects, notably renal toxic effects due to increased renal retention.[14]

Radium 223: TαT Clinical Proof of Concept

The first approved TαT to treat cancer was radium 223.[4,37,38] As a calcium mimetic, cationic radium 223 is actively incorporated into hydroxyapatite [$Ca_5(PO_4)_3OH$],[14] an integral component of the inorganic bone matrix, and delivers ionizing radiation to areas of increased osteoblastic activity (**Table 1**).[4,14,39-48] Radium 223 is typically produced in a generator from actinium 227 (half-life, 21.7 years). Radium 223 has a half-life of 11.4 days and emits 4 alpha particles via its decay chain scheme (eFigure, A in the Supplement).[48] Ninety-four percent of the total decay energy of radium 223 is emitted as alpha particles.

Because the actinium 227 precursor has a half-life of 21.7 years, large amounts of radium 223 can be efficiently produced over the

Table 1. Rates of Overall Survival of Approved Radionuclide Therapies

Approved Radionuclide Therapy	Data on Overall Survival
Alpha particle emitter	
Radium 223 for prostate cancer	
Parker et al,[4] 2013 (phase 3)	14.9 mo (radium 223) vs 11.3 mo (placebo) (HR, 0.70; 95% CI, 0.58-0.83; $P < .001$)
Beta particle emitter	
Strontium 89 for prostate cancer	
Porter et al,[39] 1993 (phase 3)	6.3 mo (strontium 89) vs 7.9 mo (placebo) ($P = .60$)
Sciuto et al,[40] 2002 (phase 3)	9.0 mo (strontium 89) vs 6.0 mo (placebo) ($P = .30$)
Quilty et al,[41] 1994 (phase 3)	8.3 mo (strontium 89) vs 7.0 mo (XRT) ($P = .10$)
Oosterhof et al,[42] 2003 (phase 3)	7.2 mo (strontium 89) vs 11.0 mo (XRT) ($P = .046$)
Yttrium 90 (anti-CD20) for NHL,[43] 2013	Effect on overall survival not known
Iodine 131 (anti-CD20) for NHL,[44] 2012	Effect on overall survival not known
Samarium 153 for prostate cancer	
Collins et al,[45] 1993 (phase 1/2)	9.0 mo (92.5 MBq/kg) vs 6.0 mo (37 MBq/kg)
Resche et al,[46] 1997 (phase 3)	No difference between 18.5 and 37 MBq/kg of samarium 153
Lutetium 177 for GEP-NETs	
Strosberg et al,[47] 2017 (phase 3)	PFS: NR (lutetium 177; 95% CI, NE-NE) vs 8.5 mo (placebo; 95% CI, 5.8-9.1) (HR, 0.21; 95% CI, 0.13-0.32; $P < .001$); overall survival: NR (lutetium 177; 95% CI, 31.0-NE) vs 27.4 mo (placebo; 95% CI, 22.2-NE) (HR, 0.52; 95% CI, 0.32-0.84; $P = .004$)

Abbreviations: GEP-NETs, gastroenteropancreatic neuroendocrine tumors; HR, hazard ratio; NE, not evaluable; NHL, non-Hodgkin lymphoma; NR, not reached; PFS, progression-free survival; XRT, external radiotherapy.

long term.[48] The 11.4-day half-life of radium 223 allows sufficient time for preparation, distribution, and patient administration.[49]

Dual Mode of Action of Radium 223

Radium 223 represents the most studied TαT in preclinical and clinical settings and exemplifies the mechanism of action of TαT. In animal models, radium 223 exhibits a dual mode of action that interferes with the progression of bone metastatic disease in advanced prostate cancer.[5] Prostate cancer cells alter bone structure and stability by modifying osteoblast function to stimulate abnormal bone formation, resulting in fragile, disorganized bone that contributes to skeletal-related events and affects overall survival.[5,50,51] The accumulation of radium 223 in the tumor microenvironment suppresses tumor-induced abnormal bone formation and induces tumor cell death.[5] The rapid decay cascade of radium 223 and its alpha particle–emitting daughter isotopes is cytotoxic to both malignant cells and bone cells in osseous metastases.[3] Studies in mice have shown that less than 1% of radium 223 decay products migrate away from the bone, thereby limiting the toxic effects and maximizing the exposure of bone metastases to alpha particle radiation.[3]

Exposure to radium 223 has been shown to induce immunogenic modulation in tumor cells and antigen-specific T-cell responses in vitro.[16] Exposure of human prostate, breast, and lung carcinoma cell lines to radium 223 resulted in the upregulation of HLA-ABC antigen and calreticulin and a significant increase in T-cell–mediated killing of carcinoma cells.[16] The ability of radium 223 to promote immunogenic modulation in tumor cells and enhance T-cell–mediated cell lysis across human tumor cell lines suggests broad applicability and a potential for combination with immuno-oncology agents.

Approval of Radium 223 for the Treatment of Prostate Cancer With Bone Metastases

Radium 223 is the first TαT approved for the treatment of castration-resistant prostate cancer (CRPC) with bone metastases.[38,52] Patients receive 6 slow intravenous injections lasting up to 1 minute at a dose of 55 kBq/kg every 4 weeks.[4,37] Based on the results from the phase 3 ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial that enrolled 921 patients, radium 223 treatment in combination with the best standard of care resulted in significant improvement in overall survival compared with placebo plus best standard of care, with median overall survival of 14.9 months in the radium 223 arm (11.3 months in the placebo arm) conferring a 30% reduction in the risk of death (hazard ratio, 0.70; 95% CI, 0.58-0.83; $P < .001$) (Table 1).[4,39-47] Overall, radium 223 treatment was well tolerated and demonstrated a good safety profile attributed to its short alpha particle range and localized delivery. Aside from infrequent all-grade thrombocytopenia (12% of patients who received radium 223 and 6% of patients who received placebo) and all-grade neutropenia (5% of patients who received radium 223 and 1% of patients who received placebo), hematologic safety was similar between radium 223 and placebo. Long-term follow-up of patients in the ALSYMPCA trial demonstrated that radium 223 treatment continued to be well tolerated, with minimal myelosuppression and conservation of hematopoietic function.[53] Secondary primary malignant neoplasms, defined as histologically different from the primary cancer, occurred in 5 patients treated with radium 223 (1 had carcinoma of unknown origin, 1 had squamous cell carcinoma, 1 had intestinal adenocarcinoma, and 2 had skin neoplasms) and in 2 placebo-treated patients (1 had a neoplasm of unknown origin and 1 had gastric cancer). In particular, patients treated with radium 223 did not develop new primary bone cancer during the 3-year follow-up.[53] A longer follow-up period (≤7 years) is being investigated in an observational study.[54]

Ongoing and Recent Studies of Radium 223

The potential of radium 223 in combination with other agents is under investigation across a range of advanced cancers. Currently, radium 223 is being tested in 2 large phase 3 trials in combination with novel antihormonal agents in the chemotherapy-naive setting of asymptomatic or mildly symptomatic prostate cancer with bone metastases.[55,56] Recently, a phase 3 randomized clinical trial of radium 223 vs placebo, each in combination with abiraterone acetate plus prednisone for chemotherapy-naive patients with asymptomatic or mildly symptomatic CRPC with bone metastases (ERA 223; NCT02043678), was prematurely unblinded.[57] The independent data monitoring committee recommended unblinding the trial owing to the observation of more fractures and deaths in the combination treatment arm. Unblinded data from the study are currently being analyzed to confirm the preliminary findings of the independent data monitoring committee. Given these results from the ERA 223 trial, the current recommendation is not to combine radium 223 with abiraterone acetate and prednisone.[57] The phase 3

Table 2. Targeted Alpha Therapies Being Investigated in Ongoing Clinical Trials

Isotope and Targeting Mechanism	Tumor Type or Indication	Phase
Radium 223		
Molecular mediated	Prostate cancer	1-3
Molecular mediated	Breast cancer	2
Molecular mediated	Multiple myeloma	1/2
Molecular mediated	Renal cell carcinoma	1/2
Thorium 227		
Monoclonal antibody	NHL	1
Actinium 225		
Monoclonal antibody	Multiple myeloma	1
Monoclonal antibody	Prostate cancer	1
Monoclonal antibody	AML	1/2
Astatine 211		
Monoclonal antibody	AML, ALL, and MDS	1/2
Lead 212		
Monoclonal antibody	*ERBB2/HER2*-positive tumors	1

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma.

PEACE III (Prostate Cancer Consortium in Europe) trial evaluating radium 223 in combination with enzalutamide for patients with mildly symptomatic or asymptomatic metastatic CRPC (mCRPC) is ongoing.[56] The results of the phase 2, prospective eRADicAte (A Prospective Evaluation Combining Radium-223 Dichloride and Abiraterone Acetate Plus Prednisone in Patients With Castration-Resistant Prostate Cancer) study of radium 223 in combination with abiraterone acetate plus prednisone for patients with mCRPC have recently been published.[58] Of the 36 patients participating in the open-label study, 96% reported adverse events that were grade 1 or 2, with the most frequently reported adverse events being diarrhea (17%), nausea (17%), and fatigue (14%). Safety follow-up occurred at the end of treatment, which was 30 days after the final administration of radium 223. Furthermore, neither the REASSURE noninterventional study (Ra-223 Alpha-Emitter Agent in Safety Study in mCRPC Population for Long-term Evaluation) nor the US and international expanded access programs indicated that the combined use of abiraterone acetate and radium 223 resulted in increased numbers of reported adverse events.[59-62] The optimal timing of TαT administration with other cancer therapies that affect bone pathophysiologic characteristics remains to be fully understood, and some combinations may be better suited for layering of treatment as opposed to simultaneous initiation.

An open-label phase 2a study showed that radium 223 treatment demonstrated clinical activity as a single agent with a well-tolerated safety profile for patients with bone-predominant breast cancer.[63] Studies of other cancer types, such as renal cell cancer and multiple myeloma, are ongoing (**Table 2**).[64,65]

Current TαT Landscape

With the overall survival benefit conferred by radium 223 treatment and its subsequent approval for bone-predominant mCRPC, interest in the therapeutic potential of alpha particle–emitting radionuclides is increasing. Other alpha particle emitters being investigated in preclinical and clinical studies include thorium 227, actinium 225, bismuth 213, astatine 211, and lead 212 (Table 2).

Thorium 227

Thorium 227 is an alpha particle emitter with a physical half-life of 18.7 days.[26] The thorium 227 decay scheme is initiated by its alpha decay into radium 223, which subsequently follows the decay chain of radium 223 (eFigure, A in the Supplement). As thorium 227 decays to stable lead 207, 5 alpha particles are released, making thorium 227 an attractive candidate for TαT.[26] Targeted thorium 227 conjugates are being investigated in several preclinical and phase 1 studies across tumor types, including prostate cancer, colorectal cancer, gastric cancer, ovarian cancer, non-Hodgkin lymphoma, and leukemia.[20-26] Thorium 227 can be readily conjugated to mAbs targeting different cell-surface antigens across tumor types and has demonstrated in vitro and in vivo antitumor activity.[20,22-26] Thorium 227 conjugated to an anti-CD22 mAb is currently being investigated in an open-label phase 1 trial for patients with relapsed or refractory CD22-positive non-Hodgkin lymphoma to determine safety and the maximum tolerated activity.[21]

Actinium 225

The decay of actinium 225 results in the emission of 4 alpha particles, which marks actinium 225 as an attractive and potent choice for TαT.[12] Actinium 225 has a physical half-life of 9.92 days and yields 3 daughter radionuclides that each emit an alpha particle on their decay (eFigure, B in the Supplement). As with radium 223, the relatively long half-life of actinium 225 allows for centralized production, distribution, and administration of actinium 225 TαT.[12,66] Another distinct advantage of actinium 225–based TαT is the emission of a 440-keV γ-ray after the decay of the bismuth 213 daughter radionuclide, which can be used for imaging to determine biodistribution.[14] An ongoing phase 1/2 trial of actinium 225–lintuzumab targeting CD33-positive myeloid leukemia cells in patients with acute myeloid leukemia has shown that treatment is safe.[27,67] The first-in-human study of actinium 225–prostate-specific membrane antigen 617 in 14 heavily pretreated patients with end-stage mCRPC showed that a treatment activity of 100 kBq/kg was tolerable and had promising antitumor effects in 9 of 11 evaluable individuals.[28] Noteworthy antitumor activity was observed in 82% of patients as assessed by radiologic response, and 75% of patients showed a decrease in the level of prostate-specific antigen, warranting further investigation in clinical trials with larger patient cohorts.

Bismuth 213

Bismuth 213 has a short physical half-life of 45.6 minutes and is prepared for therapeutic use in an actinium 225 and bismuth 213 generator.[68] The generator produces bismuth 213 that is clinically useful for 10 days.[30] Bismuth 213 decays to stable bismuth 209 through the emission of an alpha particle and 2 beta particles (eFigure, B in the Supplement). Bismuth 213 is readily conjugated to mAbs, peptides, and small molecules and has been investigated as a TαT in several clinical trials.[12,29,69] However, its short half-life and conjugation chemistry restrict the use of bismuth 213 for patients.[66] Despite these practical limitations, clinical trials have shown promising efficacy of bismuth 213. In a phase 1 study, Jurcic et al[69] used bismuth 213 conjugated to the humanized anti-CD33 antibody HuM195 (lintuzumab), which targets myeloid leukemia cells, to treat 18 patients. Injection of bismuth 213–CHX-

A-DTPA-HuM195 did not result in toxic effects associated with the infusions.[69] In a phase 1/2 study investigating the treatment of 31 patients with newly diagnosed or relapsed or refractory acute myeloid leukemia with cytarabine followed by bismuth 213–HuM195, the treatment was shown to be tolerable and was able to produce remissions in patients.[68] However, myelosuppression was the most common toxic effect associated with treatment. This clinical proof of concept for the use of bismuth 213 as a viable TαT has encouraged further investigation for patients with non-Hodgkin lymphoma, melanoma, and glioblastoma.[14]

Astatine 211

Astatine 211 has a physical half-life of 7.2 hours and decays through a branched pathway, with each decay path producing an alpha particle as it decays to stable lead 207 (eFigure, C in the Supplement).[18] Astatine 211 has several attractive features for use as a TαT, including no long-lived alpha particle–emitting daughter radionuclides,[18] photon emission that allows imaging, and compatibility for conjugation with several carrier molecules to allow targeted delivery.[18,66] The availability of astatine 211 is limited by its short half-life, which makes it difficult to deliver sufficient quantities of astatine 211 to distant treatment centers and has limited the number of preclinical and clinical studies of this radionuclide.[18,66]

Astatine 211 can be used to radiolabel mAbs[33] and small molecules, including thymidine analogues,[32] biotin analogues, and bisphosphonate complexes.[14,18] To date, astatine 211 has been investigated in 2 phase 1 clinical trials.[33,70] Treatment with chimeric antitenascin mAb 81C6 (ch81C6) labeled with astatine 211 (astatine 211–ch81C6) for 18 patients with recurrent malignant brain tumors resulted in minimal toxic effects, with no dose-limiting toxic effects after administration of single activities of up to 347 MBq.[33] Astatine 211–ch81C6 treatment also resulted in promising survival in this phase 1 trial. The second phase 1 trial demonstrated that astatine 211–labeled MX35 $F(ab')_2$ could be safely administered, without observed toxic effects, for 9 patients with advanced ovarian cancer.[70] However, several studies of astatine 211–labeled compounds of interest have been halted owing to the lack of in vivo stability of these compounds.[18] Premature release of unbound astatine 211 in vivo has been observed, which can result in irradiation of nontarget tissues, including physiological accumulation in the thyroid and stomach.[18] To avoid toxic effects, highly stable astatine 211–labeled compounds must be developed for further study.

Lead 212

Lead 212 is a beta particle emitter with a physical half-life of 10.2 hours; it is the immediate parental radionuclide of bismuth 212.[12] Bismuth 212 decays to stable lead 208 through the emission of 1 alpha particle and 1 beta particle[12] (eFigure, D in the Supplement). The first phase 1 trial investigating the administration of lead 212 conjugated to trastuzumab for patients with *ERBB2*/*HER2*-positive ovarian cancer showed minimal toxic effects.[31] In addition, there was limited redistribution of lead 212–TCMC [*S*-2-(4-isothiocyanatobenzyl)-1,4,7,10-tetraaza-1,4,7,10-tetra (2-carbamoylmethyl)cyclododecane)]–trastuzumab outside the peritoneal cavity, further demonstrating its safety.[31]

Challenges and Optimization for Future Clinical Study

The concept of TαT for cancer treatment has been discussed for decades. Targeted alpha therapy combines the affinity and specificity of molecular targeting with potent, cytotoxic alpha particle emissions to deliver systemic, high-energy radiation selectively to cancer cells and the tumor microenvironment to control cancer. Because there are no known resistance mechanisms to alpha particle radiation that have been documented, TαT represents a different treatment approach and provides an avenue of treatment to bypass mechanisms of acquired resistance in selected tumors. Furthermore, the evident rationale for combining TαTs with other oncology agents (eg, immune checkpoint inhibitors, DNA damage repair pathway inhibitors, or T-cell–based immunotherapy) allows for a multifaceted approach to cancer treatment.

Malignant cells may, however, develop resistance to a particular mechanism of delivery. For instance, prostate cancer tumor cells could evolve to downregulate surface prostate-specific membrane antigen expression on the cell in response to antibody-mediated or small-molecule–mediated TαT, thereby rendering continued therapy less effective. The development of novel radionuclide conjugation strategies will be required to overcome targeting limitations due to acquired resistance and address the problem of tumor types that have a low physiological uptake of radionuclides.

Conclusions

As an emerging treatment approach, TαT provides the possibility to bypass mechanisms of acquired resistance in selected tumors. The clinical success (established efficacy and favorable safety profile) of the first TαT, radium 223, in treating mCRPC with bone metastases has demonstrated the proof of concept for TαT. Future studies investigating more TαT options may lead to additional treatment approaches for many cancer types.

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Acquisition, analysis, or interpretation of data: Parker, Shore, Levy, Noordzij, Park, Saad.
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