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ORIGINAL ARTICLE

Why bother with alpha particles?

A. Paden King[1,2] · Frank I. Lin[1] · Freddy E. Escorcia[1,2]

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Abstract
The approval of $^{223}RaCl_2$ for cancer therapy in 2013 has heralded a resurgence of interest in the development of α-particle emitting radiopharmaceuticals. In the last decade, over a dozen α-emitting radiopharmaceuticals have entered clinical trials, spawned by strong preclinical studies. In this article, we explore the potential role of α-particle therapy in cancer treatment. We begin by providing a background for the basic principles of therapy with α-emitters, and we explore recent breakthroughs in therapy with α-emitting radionuclides, including conjugates with small molecules and antibodies. Finally, we discuss some outstanding challenges to the clinical adoption of α-therapies and potential strategies to address them.

Introduction

There has been a resurgence of interest in radiopharmaceutical therapy (RPT) for cancer treatment, with three RPTs—[^{177}Lu]Lu-DOTATATE (NCT01578239), [^{131}I]Iobenguane (NCT00874614), and $^{223}RaCl_2$ (NCT00699751)—recently demonstrating overall survival benefit and receiving FDA approval [1–3]. Treament with [^{177}Lu]Lu-PSMA-617 was compared to standard of care in the phase III VISION trial in men with metastatic castration-resistance prostate cancer (mCRPC) and demonstrated an overall survival benefit [4]. Over a dozen more agents are currently in clinical trials, including radioconjugates of small molecules, antibodies, and nanoparticles [5]. These conjugates have high tumor specificity and potency, unlike many traditional chemotherapeutics. Recent advances, built upon decades of preclinical studies, have demonstrated the therapeutic efficacy of α-emitting radionuclides, leading to the first FDA approval of an α-particle therapeutic, $^{223}RaCl_2$, for bone-limited mCRPC in 2013. The success of $^{223}RaCl_2$ has reinspired further research into α-particle-emitting radioconjugates using radionuclides such as ^{225}Ac, ^{212}Pb, ^{227}Th, ^{213}Bi, and ^{211}At. Herein, we introduce the premise of molecular radiotherapy, detailing the features that make α-emitting nuclides ideal for this application.

The basic principle of using targeted radiation for cancer treatment is simple: deliver cytotoxic ionizing radiation that causes single-strand and double-strand breaks in the DNA of a cancer cell, and subsequent cell death, while limiting damage to healthy tissues [6]. However, this concept has proven difficult in application, and even clinically approved radiopharmaceutical therapies have faced an uphill battle for widespread clinical implementation. Radiotherapy has been employed successfully for over a century with the first external beam radiation therapy being developed shortly after the discovery of the X-ray [7]. While effective at improving outcomes for patients with various types of cancers at early and oligometastatic stages, external radiation cannot definitively treat widely disseminated disease. In contrast, parenterally administered radionuclides can be selectively targeted to cancerous cells, delivering therapeutic radiation doses to numerous sites of metastases. Molecular radiotherapy can be reduced to two main components that must be considered: the choice of biomolecule used as the tumor-targeting vector, and the emission: typically, α-particle, β^--particle, or Auger electrons. By carefully selecting and optimizing these components, researchers can develop RPT to improve the outcomes of cancer patients. In this article, we focus on the development of α-particle radiopharmaceuticals, description of their properties, suitability for incorporation into radioconjugates, and key advances in the field of α-RPT.

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✉ Freddy E. Escorcia
freddy.escorcia@nih.gov

[1] Molecular Imaging Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20817, USA

[2] Radiation Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20817, USA

Physical properties and anticancer mechanisms of radiotherapeutics

The decay characteristics of α-emitting radionuclides, namely their impressive cytotoxic potential and no known mechanism of cellular resistance, make them compelling for RPT. It is estimated that several hundred β^- traversals through the nucleus are required to induce cell death, while less than ten α-decays can achieve the same result [8]. This incredible efficacy arises from the higher linear energy transfer (LET) of α-particles compared to β^- -particles. Auger emitters have high LET and shorter range than either α- or β^--particles, requiring internalization and localization to the nucleus to have a therapeutic effect [9]. α-particles deposit all their energy over a distance of a few cell diameters, whereas β^--particles may pass completely through cells without interacting with cellular components and without depositing any energy within a cell, as shown in Fig. 1. The anticancer mechanism of α-particles also supports their use for RPT. DNA damage by α-particles is multi-faceted and includes indirect damage via reactive oxygen species (ROS) or direct damage with resulting double-strand DNA breaks, DNA cross-linking, and complex chromosomal rearrangement [10]. The propensity of α-particles to cause catastrophic double-strand DNA breaks is a well-documented signature therapeutic effect [11, 12]. Conversely, β^--particles cause mostly single-strand DNA breaks. Unsurprisingly, double-strand breaks are more challenging to repair than single-strand breaks, and the more induced, the higher the probability of cell kill [13]. Additionally, recent studies show that the cytotoxic effects of α-particles can activate antitumor immune responses, further increasing their potency beyond the initial cytotoxic insult [14]. Finally, α-particles have a penetration depth through tissue of only 40–100 µm, much shorter than the up to 12-mm penetration depth of β^--particles. If one successfully localizes an α-emitter to the tumor via a targeting vector, the shorter range can theoretically result in less collateral damage to healthy tissues, increasing the therapeutic index [15]. However, this shorter range limits the "cross-fire" effect of α-particles, which is advantageous in β^--particle therapies.

The cytotoxicity of α-emitters renders them less susceptible to the development of resistance than traditional chemotherapeutics or even β^--emitters [16, 17]. Recent clinical studies have demonstrated that α-emitting radioconjugates can be used successfully as a salvage therapy after failure of β^--emitting RPTs. For instance, in patients with neuroendocrine cancers refractory to treatment with the β^--emitting [^{177}Lu]Lu-DOTATATE, subsequent treatment with [^{225}Ac]Ac-DOTATATE induced an antitumor response in some patients [18]. Similar results were observed when prostate cancer patients refractory to treatment with [^{177}Lu]Lu-PSMA-617 were treated with [^{225}Ac]Ac-PSMA-617 [19, 20]. In both the PSMA and DOTATATE examples, simply switching to the α-emitter, while keeping the targeting ligand constant, overcame resistance and improved response in some patients. Although randomized controlled trials are needed to definitively conclude a benefit, these studies suggest that α-particle therapy represents at least a promising salvage treatment following β^--therapy.

In addition to the observed lack of resistance to α therapies, the anticancer mechanisms of α-emitters have also been investigated in vitro [17, 21]. Although these studies are complicated by the hazards associated with long-lived α-emitters and the challenges of accurately estimating absorbed radiation doses on cellular and subcellular levels, several key insights have been gained into α-particle toxicity and resistance. One recent preclinical study showed that the α-emitter $^{223}RaCl_2$ exhibited 10× more potency than the γ-emitter ^{137}Cs, which primarily induces cell death via the generation of ROS [17]. Further experimentation demonstrated that α-therapy was not cross-resistant with ^{137}Cs. Cells with very high resistance to γ-radiation remained

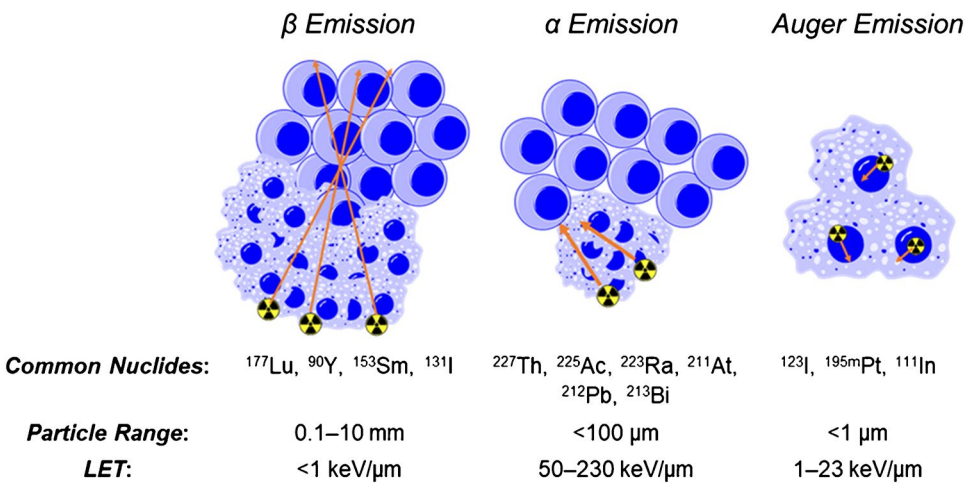


Fig. 1 Relative LET and path lengths of the three classes of therapeutic radionuclides

sensitive to α-emissions. Mutations in cellular antioxidant response proteins Nrf2 and KEAP1 greatly increased the effectiveness of α-therapy indicating their presence may represent biomarkers for α-RPT. The same gain-of-function Nrf2 mutations conferred resistance to γ-radiation. Another study explored the effectiveness of the α-emitter ^{223}Ra in cell lines with varying mutations that affect DNA repair pathways [22]. This study found that cell lines with mutations in *BRCA2* or *ATM* were especially sensitive to α-radiation, and suggests that inhibition of DNA-damage repair pathways could augment treatment response. In addition to causing double-strand DNA breaks, α-emitters have been shown to induce cell-cycle arrest and inhibit DNA synthesis in vivo [23]. A follow-up study demonstrated that the combination of the same α-therapy with gemcitabine could prevent G2-arrest and increase cell death [24].

A unique advantage of most radioconjugates, including α-emitters, is their natural pairing with complementary diagnostic imaging. One direct benefit of this "theranostic" approach resides in optimal patient selection and subsequent monitoring of patients following RPT. Patients may be first injected with a diagnostic molecule, such as [^{68} Ga] Ga-DOTATATE, to assess disease status prior to treatment with an α-emitter DOTATATE conjugate, for example. In some cases, the same element can be used for both diagnosis and therapy, for example the β^--emitter ^{212}Pb (in vivo generator of α-emitter ^{212}Bi) is used for therapy and its matched element ^{203}Pb is useful for diagnostic purposes via SPECT imaging [25]. This approach allows for monitoring of the radioconjugates' biodistribution as well as real-time tracking of the patients' treatment response. Finally, some α-emitting nuclides (or their daughters) may be imaged directly. Several recent studies have focused on SPECT imaging of X-ray and γ-emissions of ^{225}Ac, ^{227}Th, ^{223}Ra, and their daughters [26–28]. The broader application of this approach remains uncertain due to the inherently low sensitivity of SPECT and the low activities needed for RPT. The use of partner β^+-emitting isotopes having biodistribution patterns at least partially similar to α-emitters (e.g., ^{18}F and ^{223}Ra) may be helpful and warrant study [29, 30].

Hundreds of α-emitting radionuclides are theoretically accessible, but only a few have suitable half-lives and realistic production to make them potentially useful for clinical RPT. These radionuclides are ^{227}Th, ^{223}Ra, ^{225}Ac, ^{212}Pb, ^{211}At, ^{149} Tb, and ^{213}Bi. All have unique properties that make them advantageous for combination with different targeting moieties. Detailed information on the physical properties and relevant information for these commonly used α-emitting nuclides are presented in Table 1. Broadly, these radionuclides may be categorized according to half-life, with ^{227}Th, ^{225}Ac, and ^{223}Ra having half-lives > 10 days, while ^{212}Pb, ^{211}At ^{149} Tb, and ^{213}Bi all have half-lives < 12 h.

Conventionally and optimally, the half-life of the isotope is matched to the half-life of the biomolecule to which they are coupled. Accordingly, the short half-life radioisotopes are considered better partners for small molecules, and long-lived isotopes are considered better partners for antibodies, which have long biological half-lives (Table 1). However, preclinical and clinical studies have shown that ^{225}Ac radioconjugates with small molecules are also therapeutically effective, if inefficient.

$^{223}RaCl_2$: first-in-class α-particle RPT

Unconjugated radionuclides, such as ^{131}I, are some of the oldest and most successful RPTs. These therapies rely on the radionuclide's intrinsic localization to specific cancerous cells. The only "free" α-emitter to have clinical or preclinical success is ^{223}Ra. Although naturally occurring radium was first used therapeutically over a century ago [32], $^{223}RaCl_2$ only gained FDA approval in 2013 [3, 33, 34]. ^{223}Ra localizes naturally to newly forming bone, including sites of metastases, due to its chemical similarity to Ca^{2+}. ^{223}Ra improved overall survival in patients with bone-limited mCRPC with an acceptable toxicity profile. Clinical trials

Table 1 α-emitting nuclides and their physical properties

Nuclide	Half-life	Decays per atom	Imageable emissions	Notable daughters	Diagnostic partners	Source
^{227}Th	18.7 days	5α, 2β^-	84, 95, 236 270 keV γ-rays	^{223}Ra (11 d $t_{1/2}$) ^{219}Rn (gas)	^{111}In, ^{89}Zr	^{227}Ac generator
^{223}Ra	11.4 days	4α, 2β^-	84, 95, 270 keV γ-rays	^{219}Rn (gas)	^{18}F, ^{99m}Tc	^{227}Ac generator
^{225}Ac	9.9 days	4α, 2β^-	218, 440 keV γ-rays (from ^{213}Bi daughter)	^{213}Bi (45 m $t_{1/2}$)	^{111}In	^{229}Th generator, accelerator
^{212}Pb	10.6 h	1α, 2β^-	440 keV γ-ray	^{213}Bi (45 m $t_{1/2}$)	^{203}Pb	^{224}Ra generator
^{211}At	7.2 h	1α, 1EC	~85 keV X-ray	^{207}Bi (32 y $t_{1/2}$)	^{124}I, ^{123}I	α-Particle cyclotron
^{149} Tb	4.1 h	0.17α, 0.83β^+	Multiple parent and daughter emissions	^{145}Eu (5.9 d $t_{1/2}$) ^{149}Gd (9.3 d $t_{1/2}$)	^{149} Tb (positron and gamma emissions)	Proton spallation, other methods [31]
^{213}Bi	46 min	1α, 2β^-	440 keV γ-ray	None	^{68} Ga	^{225}Ac generator

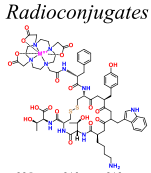
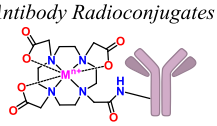
are ongoing to explore additional applications of $^{223}RaCl_2$ as a cancer therapeutic.

Despite its clinical approval and current use, several questions must be answered to optimize the efficacy of $^{223}RaCl_2$, and to understand and mitigate associated adverse events sufficiently. Several studies focusing on $^{223}RaCl_2$ are summarized in Table 2. Exploiting γ-emissions of ^{223}Ra for imaging using SPECT is possible, though at the expense of long scan times. Treatment combinations of ^{223}Ra with standard-of-care chemotherapy are being explored in a phase I/IIa trial. This trial looks to define the safety and efficacy combining ^{223}Ra and docetaxel (NCT03574571) in patients with mCRPC [35]. The phase II RAVENS trial (NCT04037358) is evaluating whether $^{223}RaCl_2$ might improve progression-free survival in men with oligometastic prostate cancer receiving stereotactic ablative radiotherapy [36]. Such studies are critical in determining which α-emitter-drug combinations are beneficial, or just as importantly, harmful [37]. For example, a recent combination study investigating the addition of ^{223}Ra to abiraterone acetate and prednisone therapy in mCRPC patients unexpectedly reported more fractures in the patients treated with the investigational arm compared with the placebo (NCT02043678) [38]. Long-term sequelae of $^{223}RaCl_2$ treatment are incompletely understood. An observational clinical study (NCT04256993) is investigating long-term efficacy and side effects in a large cohort of patients, focusing on the incidence of bone fractures in patients treated with $^{223}RaCl_2$. Collectively, results from these trials can help guide $^{223}RaCl_2$ treatment, improve patient selection, and mitigate untoward effects. Despite ^{223}Ra's effectiveness as a therapeutic drug, the potential for expanding its use in targeted radiotherapy conjugates is limited due to a lack of available in vivo compatible chelators. In a recent study, Abou et al. reported on stable ^{223}Ra chelation in vivo, which may facilitate the development of new ^{223}Ra-based conjugates using tumor-targeted vectors [39].

α-Emitter conjugates to small molecules and antibodies

Several properties outlined in the previous sections make α-emitters promising for development of conjugated RPT agents. The natural pairing of radioactive groups with cancer-targeting molecules has long been recognized. Much of the groundwork for therapeutic radioconjugates may be established using radiodiagnostics [40–44]. Unlike conventional chemotherapeutics, which must interact directly

Table 2 Categories of alpha-RPT, their properties, and relevant clinical studies

Radiotherapeutic Category	Advantages	Disadvantages	Notable Clinical Studies	Cancer Type
Unconjugated Radionuclides $^{223}RaCl_2$	• Simple to produce and test • Intrinsic localization to cancerous tissue • Proven clinical success	• Little modification possible • Limited number of potential nuclides	• $RaCl_2$ FDA-approved in 2013 [26]	• mCRPC
			• $RaCl_2$ biodistribution (Phase 1, NCT04521361)	• mCRPC
			• $RaCl_2$ side effects (NCT04256993)	• mCRPC
			• $RaCl_2$ combination with docetaxel (Phase 3, NCT03574571)	• mCRPC
			• $RaCl_2$ treatment of metastatic breast cancer (Phase 2, NCT02366130, NCT04090398)	• Breast Cancer with Bone Metastases
			• $RaCl_2$ combination with abiraterone (Phase 3, NCT02043678)	• mCRPC
Small Molecule Radioconjugates  M^{n+} = ^{225}Ac, ^{213}Bi, ^{212}Pb, ^{211}At	• Short half-life of small molecules facilitates radionuclide clearance • Concept established clinically with β⁻-emitters	• Only moderate specificity • Short-lived conjugates must be labeled onsite	• [^{212}Pb]Pb-DOTAMTATE (Phase 1, NCT03466216)	• $SSTR^+$ NET
			• [^{225}Ac]Ac-PSMA-617 (Phase 1, NCT04597411)	• mCRPC
			• [^{225}Ac]Ac-PSMA ligand (Phase 1, NCT04225910)	• mCRPC
Antibody Radioconjugates  M^{n+} = ^{227}Th, ^{225}Ac, ^{212}Pb, ^{211}At, ^{213}Bi	• Excellent binding affinity for targets • Complements unlabeled antibody therapies • High potency pairs well with low-expression targets	• Long biological half-lives require excellent chelators • Long-lived daughters may redistribute • Radiolabeling often difficult	• [^{225}Ac]Ac-aCD33 (Phase 1, NCT02998047)	• Multiple Myeloma
			• [^{225}Ac]Ac-IGF-1R (Phase 1, NCT03746431)	• $IGF\text{-}1R^+$ Solid Tumors
			• [^{225}Ac]Ac-J591 (Phase 1, NCT03276572, NCT04506567)	• mCRPC
			• [^{227}Th]Th-aMSLN (Phase 1, NCT03507452)	• $MSLN^+$ Tumors
			• [^{227}Th]Th-aCD22 (Phase 1, NCT02581878)	• Non-Hodgkin's Lymphoma
			• [^{227}Th]Th-aPSMA (Phase 1, NCT03724747)	• mCRPC
			• [^{212}Pb]Pb-aHER-2 (Phase 1, NCT01384253)	• $HER2^+$ Tumors
			• [^{213}Bi]Bi-aCD33 (Phase 1, NCT03466216)	• $SSTR^+$ NET
			• [^{211}At]At-aCD45 (Phase 1/2, NCT03670966)	• Leukemia, Myelodysplasia
			• [^{211}At]At-aCD38 (Phase 1, NCT04466475)	• Multiple Myeloma

mCRCP, metastatic castration-resistant prostate cancer; *SSTR*, somatostatin receptor; *NET*, neuroendocrine tumor; *MSLN*, mesothelin; *IGF-1R*, insulin-like growth-factor 1 receptor

with a target biomolecule (e.g., DNA, microtubules), RPT agents can induce cell death from outside the cell. This property is advantageous for target-based therapies. Cleavable linkers or cellular uptake and degradation are not necessary to induce cell death, unlike traditional small-molecule and antibody-based treatments. However, cellular uptake and retention is highly advantageous for RPTs. Cell uptake prevents daughter redistribution, and increased proximity to the cell nucleus can lead to higher cytotoxicity. Another potential advantage of radioconjugates, relative to many targeted drugs, is that they are cytocidal. This feature can transform an unlabeled targeted agent that does not have much of a therapeutic effect to a radiolabeled one that does [45]. Furthermore, efficient tumor cell kill can help mitigate development of resistance via compensatory changes (e.g., decreased availability or expression of target molecules, selection for clones with resistant mutations) following therapy.

Thus far, small-molecule radioconjugates have enjoyed the greatest clinical success, and the small-molecule conjugates that are currently clinically approved use β^--emitting nuclides, likely because these conjugates are easier to develop and more widely available than their α-emitting counterparts. However, as discussed in the previous section, α-particle-based therapies are also being explored. Somatostatin receptor (SSTR)–targeting ligands have been conjugated to DOTA or DOTA-derivative chelators to treat SSTR-expressing neuroendocrine tumors [46, 47]. Several α-emitting radionuclides have been investigated preclinically in SSTR-targeting conjugates, including ^{225}Ac, ^{213}Bi, and ^{212}Pb. Preclinical investigation of [^{225}Ac]Ac-DOTATOC showed that this conjugate has marked antitumor activity in vivo [48]. The related conjugate [^{225}Ac]Ac-DOTATATE has been investigated clinically in patients who progressed or had stable disease following treatment with [^{177}Lu]Lu-DOTATATE [18, 49]. Short-term results from this phase I trial indicate that this conjugate is well-tolerated. Early efficacy data reported 1 patient of 53 in the study with complete remission, 41 patients with partial remission, and 9 patients showing stable disease. A retrospective clinical evaluation of [^{213}Bi]Bi-DOTATOC in 8 patients showed that this conjugate is very well-tolerated and exhibited a promising antitumor response [50]. Finally, the related compound [^{212}Pb]Pb-DOTAMTATE has shown preclinical efficacy for SSTR$^+$ tumor treatment [51], and a phase I trial of this conjugate is currently underway (NCT03466216). Notably, unlike the other studies mentioned, this trial focuses on patients naive to therapy with ^{177}Lu- or ^{90}Y-labeled DOTATATE. Preliminary results indicate that the conjugate is well-tolerated and has a promising efficacy signal with two patients exhibiting complete response and one with a partial response [52].

In addition to SSTR-targeting conjugates, several studies have focused on PSMA-targeting α-particle RPTs [53]. Chelates of ^{213}Bi, ^{212}Pb, and ^{225}Ac have been conjugated to PSMA-targeting ligands. [^{225}Ac]Ac-PSMA-617 has demonstrated promising effectiveness with complete remission for 2 out of 2 patients with late-stage mCRPC as reported in a small retrospective first-in-human study [19]. Importantly, a prospective phase 1 trial of this conjugate is currently underway (NCT04597411). One prospective cohort study compared 28 mCRPC patients of whom half were refractory to [^{177}Lu]Lu-PSMA-617 treatment, whereas the other half were RPT-naïve [20]. Patients in both groups showed objective response to treatment. The dose was well-tolerated, suggesting that [^{225}Ac]Ac-PSMA-617 may be a good candidate for both front-line and second-line treatment of mCRPC. ^{212}Pb and ^{213}Bi have also been investigated with PSMA-617 and other PSMA-targeting molecules. Several studies have shown promising preclinical results in vivo using ^{212}Pb, but no clinical data has yet been collected [54]. A case report of one patient with mCRPC who exhibited cancer progression demonstrated remarkable radiographic and biochemical response after treatment with [^{213}Bi]Bi-PSMA-617 [55]. These reports are helpful in providing bioplausibility and feasibility of more systematic clinical evaluation of such agents, but the short half-life and difficulty in distribution of ^{213}Bi represent significant hurdles to further clinical development.

Antibody-based radioconjugates have been explored to augment the inherent limited therapeutic effect of tumor target-specific antibodies. Many antibody therapies currently in the clinic are unconjugated relying upon antibody-dependent cellular cytotoxicity (ADCC) to induce cell death [56]. However, ADCC alone may be insufficient for tumor eradication. This limitation has spurred a renewed excitement for antibody–drug and antibody-radionuclide conjugates. Currently, two antibody-based RPTs are FDA-approved. Both therapeutics use β^--emitters conjugated to antibodies targeting the B-cell lymphoma biomarker CD20. However, the first approved radioconjugate, [^{131}I]I-Tositumomab (Bexxar®) is no longer in production, and the second conjugate, [^{90}Y]Y-Ibritumomab (Zevalin®), has seen decreased year-over-year utilization [57–60]. Despite demonstrating durable complete responses in patients with B-cell malignancies, these agents were not broadly adopted clinically. This outcome reflects broader structural barriers to RPTs within the practice of medicine, particularly in the USA. In addition, the non-radioactive CD20-specific antibody, rituximab, has the same indication as the radioconjugates and fits more neatly with existing clinical workflows.

Two α-emitting antibody conjugates targeting the leukemia biomarker CD33 have been clinically investigated. The first paired ^{213}Bi with anti-CD33. The clinical studies showed that the conjugate induced remission in most

patients [61, 62]. Furthermore, in vitro studies of [^{213}Bi]Bi-anti-CD33 showed this conjugate was not cross-resistant with cells resistant to β^-- and γ-radiation [63]. However, the short half-life of this isotope ($t_{1/2}$ = 46 min) and difficulties in production and cost led to a shift to [^{225}Ac]Ac-anti-CD33 [64]. This second-generation CD33-targeting radioconjugate is currently in clinical trials (NCT02575963), and preliminary findings indicate it is well-tolerated and exhibits anti-leukemic activity [65, 66]. Despite the logistic and economic difficulties of implementing the [^{213}Bi]Bi-anti-CD33 conjugate, other antibody conjugates of ^{213}Bi have entered clinical trials, and preliminary results indicate that these are well-tolerated in patients. In fact, the conjugate [^{213}Bi]Bi-cDTPA-9.2.27, which targets chondroitin sulfate proteoglycan 4 (a.k.a NG2) overexpressed in melanomas, has proven to be tolerable at doses of up to 450 mCi (16.7 GBq) and shows activity in patients with melanoma [67]. Another ^{213}Bi-antibody conjugate targeting EGFR has recently been investigated in a pilot feasibility prospective clinical study for the treatment of high grade carcinoma in situ of the bladder [68]. The RPT induced complete remission in three of 12 patients with no observed adverse effects and warrants further study.

Several clinical studies have also investigated ^{211}At-labeled antibodies for RPT [69]. Notably, an older study of a ^{211}At-labeled antitenascin antibody administered intracranially to patients bearing brain tumors demonstrated a favorable treatment response with minimal toxicity [70]. More recently, a 12-year follow-up of a dose-finding study in ovarian cancer patients treated with ^{211}At-labeled antibody fragment ($F(ab')_2$) targeting SLC34A2, a cell surface glycoprotein, was reported [71]. The conjugate exhibited low toxicity and demonstrated a therapeutic response in some patients. Other clinical trials evaluating ^{211}At-labeled antibodies focusing on multiple myeloma, recurrent, refractory acute lymphocytic leukemia, and myelodysplastic disorders are currently in progress (NCT04466475, NCT03670966).

The long-lived α-emitter ^{227}Th has emerged as another option to pair with antibodies due to its ease of chelation and relatively high availability [72]. Preclinical studies of PSMA-targeting antibody conjugates with ^{227}Th have been promising, and a phase I clinical trial of one conjugate is ongoing (NCT03724747) [73]. Preclinical investigation using this conjugate showed increased tumor uptake relative to healthy tissue, as well as dose-dependent tumor inhibition in both subcutaneous tumors and a metastatic model. Notably, the study showed potential synergy between the PSMA-targeted ^{227}Th RPT in conjunction with androgen receptor antagonists. ^{227}Th-antibody conjugates targeting mesothelin (NCT03507452) and CD22 (NCT02581878) are also in clinical trials [73, 74]. A known challenge of intact antibody-based radioimmunoconjugates is hematologic toxicity in already heavily pretreated patients, which may limit their translational potential. While true for both α- and β^-- emitters, it may be more prominent in β^--emitting antibody radioconjugates due to the longer path length. Efforts to overcome these challenges include pre-targeting strategies and dose fractionation [75].

The growing body of research indicates that α-emitters can make safe, effective therapeutics when conjugated to appropriate targeting molecules. Although no α-emitting radioconjugates have received clinical approval, their high potency and tunable molecular footprint make them excellent partners for targeting antibodies or small molecules. Based on convention, t ^{213}Bi and ^{212}Pb may pair best with rapidly cleared smaller molecules, whereas ^{225}Ac and ^{227}Th may be better suited for antibodies, which clear much more slowly. Despite its relatively long half-life, ^{225}Ac has proven effective in both small-molecule and antibody conjugates, but its high toxicity due to its long half-life and daughter nuclide redistribution remains a concern.

A clinical perspective: potential and challenges for α-based RPT

Currently, there is no consensus on the proper dose, timing, administration route, or ideal chemotherapeutic combinations with RPTs—and the best approach will likely be different for each RPT and disease presentation. Any of these variables can have a profound impact on the ultimate success of the therapy. Guidelines should be established, if possible, and commonalities may emerge across the various RPT agents as a class.

Studies have shown that administering several smaller doses of the RPT over an extended period of time (fractionation) can increase the treatments' effectiveness and decrease the off-target radiation toxicity [45, 76, 77]. This approach is intuitive, as most anticancer therapeutics are administered in multiple cycles to increase tolerability and minimize side effects while maintaining efficacy. External beam radiation is similarly administered. Potential challenges, however, include the logistics inherent to a multi-dose regimen. Many radionuclides, and α-emitters in particular, are relatively scarce and are typically produced on a strict schedule. Thus, receiving frequent, regular shipments of radionuclides for patient treatment on a clinical use schedule can be challenging, especially for those with shorter half-lives. While having a six-cycle regimen is feasible for long-lived agents, such as $^{223}RaCl_2$, which has already been FDA-approved and enjoys commercial/clinical success, it is critical that radionuclide supply is able to meet the demand for clinical trials of new α-emitting RPTs.

The administration route of RPTs can also have a profound impact on the treatment. While intravenous (IV) administration is common, it may not be ideal in all cases,

especially for tumors within enclosed compartments. For example, injection of radioconjugates intraperitoneally (IP) or intracranially for tumors located in these regions may increase the tumor-absorbed dose relative to the off-target dose. In one notable, though small, clinical study, patients were treated with a [^{212}Pb]Pb-trastuzumab conjugate via IP administration [78, 79]. The radioimmunoconjugate showed confinement to the peritoneal cavity, with only 6% of the conjugate observed elsewhere. Another study showed that a ^{213}Bi-labeled radioconjugate targeting the NK-1 receptor was well-tolerated and effective in treating glioblastoma when administered intracranially [80, 81].

Further considerations for α-emitter-based RPTs include the potential for synergistic pairings with traditional chemotherapy or other targeted therapies. Because clinical studies of α-based RPTs are still few, ideal partners have not yet been established, although several promising combinations are being tested [82, 83]. In theory, RPTs should synergize with any agents that increase their uptake or the tumor's susceptibility to DNA damage, such as platinum-based drugs and taxanes. Preclinical studies have shown that these agents may augment response to α-therapies [84, 85]. Pairing RPTs with novel radiosensitizers, such as PARP inhibitors, can greatly improve their effectiveness [86]. Others have also shown that RPTs combine well with anti-angiogenic drugs and therapeutic antibodies [84]. Further analysis and careful experimentation are needed to identify ideal treatment partners, which may vary widely depending on the type, target expression profile, and stage of the cancer to be treated. In addition, high-quality, randomized controlled studies are critical to identify specific patient populations to achieve the greatest benefit from RPT treatment and provide clear treatment indications.

The future of α-therapy

α-particle-based RPT represents a compelling therapeutic modality for disseminated cancers. Combination therapies and innovative dosing strategies have emerged recently that may greatly improve upon the prior iterations of α-RPTs. Also, as α-emitting radionuclide production and distribution capacity increases, investigators can correspondingly increase our collective knowledge of this currently underexplored field.

As mentioned earlier, one of the greatest potential clinical uses of α-based RPT is as a salvage or second-line therapy in patients with disease refractory to other treatment. α-therapy has demonstrated ability to overcome cancer resistance. Its distinct mechanism of cellular toxicity and indifference to hypoxia or drug-transporter overexpression make it ideal for use in cancers with resistance to traditional treatments. Furthermore, α-emitting conjugates can also be used in combination with β^--emitters partnered with the same targeting motif or as salvage therapy following treatment failure with the β^--emitting conjugate. Additionally, α-therapy could be combined with external beam radiation to dose-escalate therapy to gross disease, while molecular RPT can address disseminated macroscopic or microscopic disease [87, 88]. This approach is particularly compelling in the setting of oligometastatic disease [36]. Finally, combination with standard-of-care anticancer treatments (e.g., chemotherapy, anti-angiogenic therapy, kinase inhibitors, immune checkpoint blockade) or exploratory agents (e.g., DNA repair pathway inhibitors) must be properly investigated for use in conjunction with α-RPT in order to find synergistic pairings, while remaining mindful of overlapping toxicities.

Pre-targeting strategies may also enhance the RPT paradigm and preclinical results have shown effective ^{225}Ac therapy using this approach [89]. Typically, the tumor-targeting moiety is administered, allowed to bind to the target with the excess cleared from the body prior to administration of the fast-clearing radioactive component, which can bind to the tumor-targeting moiety in vivo using several established methods [75, 90]. Pre-targeting has been evaluated in humans and has been shown to reduce the overall non-target radiation load on the patient while maintaining the high tumor radiation dose of traditional antibody therapy [91].

Another potential avenue for expansion of the current α-RPT is the development of imaging methods that allow for visualization of the treatment. ^{225}Ac and ^{223}Ra both have characteristic photon emissions that may be imaged via SPECT during their decays, which can faciliate accurate absorbed dose estimates. While several recent studies have focused on imaging these nuclides in vivo, the relatively low administered activities of the nuclides and the long imaging times required for SPECT may ultimately make clinical imaging difficult. Perhaps an alternative strategy is to partner α-emitting nuclides with congeners or other isotopes for imaging. For instance, ^{211}At may be combined with ^{124}I (PET) or ^{123}I (SPECT) for diagnostics imaging, and ^{212}Pb may be partnered with ^{203}Pb for SPECT. The α-emitting ^{149} Tb might offer another interesting option since it can be imaged by PET [92]. The difficult production and long-lived daughters of this nuclide have hindered clinical translation to date; however, improved production methods may increase the availability of ^{149} Tb in the near future [31].

In addition to the importance of overcoming technical challenges, it is absolutely critical that we test the most favorable agents in prospective, randomized controlled trials for definitive evaluation. Anecdotal and small single-institution series are important to demonstrate feasibility and bioplausibility; however, such studies are insufficient to move the field forward. Fortunately, as level I evidence from RCTs accumulate for β^--emitting RPTs, we can use these as templates for testing α-emitting RPTs. In addition, while it is

intuitive that personalized dosimetry in patients treated with RPTs might prove beneficial for patient safety and therapeutic efficacy, as with external beam radiotherapy, prospective studies in patients are needed to test this hypothesis [93].

The improving quality and quantity of radionuclide production, combined with increasingly available tools to identify tumor-selective targets using next-generation sequencing, enable us to engineer diverse molecules specific to cancer targets of interest. These efforts have been further facilitated by the development of new radiochelates for alpha-emitting nuclides, which may provide safer, more easily manufactured conjugates. In addition, the marked ability of targeted α-emitting agents to effectively kill cells, which may be enhanced with strategic drug combinations, coupled with no known mechanisms of resistance all suggest a promising future of α-particle RPT. Now that these advances are in place, it is up to our community of multidisciplinary investigators to do the hard work to realize the full potential of this modality and expand the cancer therapy armamentarium for patients.

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