Am J Nucl Med Mol Imaging 2025;15(6):236-250
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0167634

Review Article

Current landscape and clinical progress of targeted alpha radioimmunotherapy

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Received July 22, 2025; Accepted November 9, 2025; Epub December 15, 2025; Published December 30, 2025

Abstract: Theranostics is an interesting 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) offers a promising route to precisely targeted treatments with reduced systemic toxicity compared to conventional radiotherapy. Beta (β)-emitting isotopes (e.g., ^{131}I, ^{90}Y) have been more commonly coupled in RIT, but the use of alpha (α)-emitters (e.g., ^{225}Ac, ^{212}Pb), for RIT (α-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. However, there are several challenges to RIT. The production of daughter isotopes from α decay makes dosimetric assessments difficult and could potentially 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. Yet, there are a variety of α-RIT agents currently in development to treat prostate cancer, hematologic malignancies, and other solid tumors. Many agents show promise, like ^{227}Th-epratuzumab, a CD22-targeting antibody used in the treatment of relapsed or refractory acute myeloid leukemia (R/R AML). While notoriously deadly and difficult to treat, the disease control rate in patients with R/R AML taking ^{227}Th-epratuzumab was 38%. Like many α-RIT therapies, follow-up studies are needed to continue to improve efficacy. Strategies to widen the therapeutic indices of these agents have been investigated such as pretargeting, use of antibody fragments, chelator optimization and combination therapies. This review describes the current landscape and clinical progress of targeted α radioimmunotherapy.

Keywords: Alpha radioimmunotherapy (α-RIT), α-emitting radionuclides, monoclonal antibodies (mAbs), hematologic malignancies, prostate cancer, solid tumors

Introduction

The use of pharmaceuticals labeled with radioisotopes has become a popular strategy to treat and image multiple disease sites specifically. By using a highly specific targeting agent, radioisotopes can emit energy to induce DNA breaks and destroy tumor cells in a systemic manner that other radiation strategies cannot do [1]. These radiopharmaceuticals can also be used for imaging and diagnosing malignancies in addition to therapy, such as Food and Drug Administration (FDA)-approved PSMA-617, which can be tagged with ^{68}Ga or ^{177}Lu for imaging or therapeutic purposes, respectively [2]. The use of a single agent for both of those purposes is called theranostics. Targeting agents can take a variety of different forms such as peptides, small molecules or antibodies. Antibodies are well suited for this application due to their incredibly high targeting selectivity and their use in this context is termed radioimmunotherapy (RIT) [3].

RIT has been studied in the treatment of a variety of cancers, including hematologic malignancies, prostate cancer, glioblastomas, and other difficult-to-treat cancers. Several RITs labeled with beta (β)-emitters have been approved by FDA, including tositumomab (Bexxar) and ibritumomab tiuxetan (Zevalin), both of which treat non-Hodgkins lymphoma (NHL) [3]. β-emitting isotopes such as ^{131}I, ^{177}Lu and ^{90}Y are commonly used due to their greater availability, and their stability in ligation to monoclonal antibodies (mAbs) [4]. However, despite both theoretical and clinical promise, a common dose-limiting hurdle for RIT agents is hematopoietic toxicity [5]. This is due to the long hematological half-lives of antibodies [6], and the physical barriers antibodies face in infiltrating solid tumors, leading to small therapeutic indices [5]. Potential solutions to this include pretargeting, which separates the tumor-targeting and the payload delivery steps [5], and using alpha (α)-emitting isotopes.

Compared to β-emitters, α-emitting radionuclides have a much shorter tissue range and much higher linear energy transfer (LET) [4]. Several common β and α-emitting isotopes are listed in **Table 1**. β radiation has a longer tissue range, leading to additional lethal effects to the tumor microenvironment, which is termed the crossfire effect [4]. However, this longer tissue range leads to more toxicity to neighboring tissue [7]. Additionally, a higher LET from α particles causes larger DNA damage breaks and

Table 1. Commonly used isotopes in RIT and their physical characteristics [6, 7, 19, 57-60]

Isotopes	Emission of therapeutic interest	Half-life	Max Particulate Energy (MeV)	Approximate emission range (mm)
Lutetium-177	Beta	6.6 days	0.5	0.6
Zirconium-89	Beta	3.3 days	0.897	1.23
Indium-131	Beta	8.02 days	0.606	2.9
Yttrium-90	Beta	2.7 days	2.28	5.5
Actinium-225	Alpha	10 days	6.0-8.4	0.05-0.08
Lead-212	Alpha	10.64 hours	5.9-8.8	0.05
Astatine-211	Alpha	7.2 hours	7.45	0.05-0.08
Bismuth-213	Alpha	46 minutes	8.4	0.07-0.10
Thorium-227	Alpha	18.7 days	5.7-7.4	0.05-0.08

therefore a higher frequency of cell cycle arrest and apoptosis in tumor cells [3]. Due to these benefits and increasing availability of α-emitters, they make an attractive alternative to β-emitters in RIT (α-RIT). This review intends to provide an update on the current landscape of α-RIT agents and their clinical progress.

Key α-emitting radionuclides in clinical development

When choosing the isotope for α-RIT, it is important to consider a half-life that balances the sufficient delivery of dose to the tumor while limiting the systemic and local toxicities [3]. Another consideration with half-life is that it needs to be long enough for practical production and preparation. Therefore, radionuclides that have shorter half-lives like ^{213}Bi, ^{211}At and ^{212}Pb ($t_{1/2}$ = 46 min, 7 hr, and 10.6 hr respectively) are limited to treating tumors that are more easily accessible [8]. On the other hand, sites that are more difficult to reach require isotopes such as ^{225}Ac and ^{227}Th, which have half-lives of 10 days and 18.7 days, respectively. ^{225}Ac is the most commonly used radionuclide due to its favorable characteristics [9]. Its half-life matches well with the pharmacokinetics of antibodies and antibody fragments, and it functions as a nanogenerator in that one ^{225}Ac emits four high-energy α particles, making it highly potent. However, ^{225}Ac has production and daughter isotope limitations, which are discussed later in this review.

Disease-specific applications and clinical progress

Treatment of hematologic cancers

Because hematological tissues are extremely radiosensitive, and a cancer cell's radiosensitivity correlates with the cell of origin, hematological cancers are inherently radiosensitive [10]. So far in this application, there are a few α-RIT agents in clinical trials and more in preclinical development. The most extensively studied agent in this context is lintuzumab, which targets CD33 and is used in the treatment of relapsed or refractory acute myeloid leukemia (R/R AML). CD33 is a cell surface glycoprotein expressed at much higher levels on acute myeloid leukemia blasts compared to myeloid progenitors of healthy individuals [11, 12]. While the only treatment for AML with curative potential is allogenic hematopoietic cell transplantation (alloHCT), to increase the success rate of alloHCT, many relapsed or refractive patients undergo salvage therapy to decrease their leukemic burden before transplantation [11]. Current strategies include chemotherapy drug cocktails like CLAG-M (cladribine, cytarabine, granulocyte-colony stimulating factor, and mitoxantrone). α-RIT is a potential tool for conditioning before alloHCT with decreased possibility for extramedullary toxicity. Lintuzumab has been conjugated to ^{225}Ac for α-RIT and is currently undergoing phase I studies for the treatment of R/R AML [12].

In this phase I trial, eighteen patients received a single infusion of ^{225}Ac-lintuzumab between the doses of 18.5 and 148 kBq/kg to determine safety and clinical activity [12]. Patients were also administered an unlabeled dose of lintuzumab to decrease first pass binding of labeled antibody in the liver. No patient experienced remission, but antileukemic effects were seen at all dose levels. Bone marrow blasts were reduced in 67% of patients across all dose levels, while peripheral blood blasts were reduced in 63% of patients receiving at least 37 kBq/kg. However, there was no correlation between injected activity and blast reduction, which may be due to the small number of patients. The maximum tolerated dose (MTD) was determined to be 111 kBq/kg, with myelosuppression and infection complications being dose-limiting. Another notable adverse effect was hepatic toxicity as 3 patients (17%) experienced grade 3 or higher liver function abnormalities [12]. Further studies are needed to continue to evaluate the efficacy and safety of this agent.

Several studies were also completed with the labeling of lintuzumab with ^{213}Bi. In a phase I dose escalation study, seventeen patients with R/R AML were treated with 10.36 to 37.0 MBq/kg of ^{213}Bi-lintuzumab [13]. All evaluable patients experienced myelosuppression that recovered, with no significant extramedullary toxicities. Of the fifteen evaluable patients, 14 had a reduction in bone marrow and circulating blasts. The median response duration was 19 days for these patients, but none of them experienced remission. Despite this, this study demonstrated safety and preliminary efficacy of ^{213}Bi-lintuzumab.

A direct comparison of ^{225}Ac-lintuzumab and ^{213}Bi-lintuzumab reveals significantly greater potency for the ^{225}Ac-labeled agent. Most patients achieved blast reduc-

tion at doses of 37 kBq/kg of ^{225}Ac-lintuzumab, compared to the much higher 10.36-37 MBq/kg required for the ^{213}Bi-labeled agent. This enhanced potency, however, comes with increased toxicity. The MTD for ^{225}Ac-lintuzumab was 111 kBq/kg, substantially lower than the 37 MBq/kg MTD for ^{213}Bi-lintuzumab. Furthermore, while both agents caused myelosuppression, ^{225}Ac-lintuzumab was uniquely associated with hepatic toxicities, whereas ^{213}Bi-lintuzumab exhibited no extramedullary toxicities. These differences are likely due to ^{213}Bi's much shorter half-life and the "nanogenerator" property of ^{225}Ac, which releases multiple α particles over time. Consequently, ^{213}Bi-labeled agents may be better suited for combination therapies, while ^{225}Ac-labeled agents show promise as a potent monotherapy for AML.

Similarly, the anti-CD45 antibody BC8-B10 has been labeled with ^{211}At and used in phase I/II clinical trials to condition patients undergoing HCT with either malignant or nonmalignant disease. Both trials of the treatment of patients with nonmalignant disease (NCT04083183) and with malignant disease (NCT03670966) are recruiting now.

Another agent in early clinical trials is a ^{227}Th labeled epratuzumab (BAY 1862864). Epratuzumab is a humanized anti-CD22 antibody that has previously been conjugated with ^{90}Y and studied in phase III trials. CD22 is a B-cell specific immunoglobulin that functions as a negative regulator of B-cell receptor signaling [14]. It is expressed on the majority of relapsed or refractory non-Hodgkin's lymphoma (R/R-NHL) while absent on stem cells, plasma cells and B cell progenitor cells. ^{227}Th-epratuzumab has been evaluated in a dose escalation phase I study in patients with R/R-NHL (NCT02581878) [14]. 21 Patients underwent four treatment cycles at a starting dose of 1.5 MBq, with escalations of 1.5 MBq until MTD was reached or an active dose was determined. The dose levels used exhibited acceptable toxicity, with no dose-dependent or accumulative toxicity observed. In terms of efficacy, across all dose ranges, a total overall response rate (ORR, complete response and partial response) was 25% and the disease control rate (CR, PR, and stable disease) was 38%. However, the small sample size, heterogeneity of disease in the sample, and early termination of the trial due to non-safety or efficacy reasons prevent proper response rate evaluation for ^{227}Th-epratuzumab.

Daratumumab is a first-in-class anti-CD38 antibody approved for use in the treatment of newly diagnosed and relapsed or refractory multiple myeloma (R/R MM) [15]. CD38 is a transmembrane glycoprotein present on many hematopoietic cells and is overexpressed in MM plasma cells [16]. However, some MM patients have low CD38 expression, reducing daratumumab's efficacy, which is where α-RIT can increase potency. After showing preclinical promise, ^{225}Ac-DOTA-daratumumab in combination with cold daratumumab is currently in a phase I trial that is currently recruiting patients with R/R MM (NCT05363111).

While treatment and conditioning of patients with hematologic cancers are the most clinically studied application of α-RIT, there are still questions about its safety. There are many clinical trials in progress, as seen listed in **Table 2**, but finding ways to widen the therapeutic index of these agents is critical for further clinical progress.

Treatment of metastatic castration-resistant prostate cancer

Metastatic castration-resistant prostate cancer (mCRPC) remains incurable with a median survival of less than three years [17]. There are several α-RIT agents that target prostate specific membrane antigen (PSMA) that are in the middle of clinical trials, with some early results reported. PSMA is a well-established therapeutic target due to its high expression on the plasma membrane of prostate cancer cells and low expression on healthy tissues. J591 is a deimmunized monoclonal antibody that targets PSMA and, when tagged with ^{177}Lu, has demonstrated acceptable toxicity, good antitumor efficacy and is currently being evaluated further in a phase III clinical trial (NCT04876651) for patients with mCRPC [18]. Due to the hypothesized benefits of α-emitters, preclinical studies were carried out with ^{213}Bi-J591, and showed promise, leading to a phase I dose-escalation study with ^{225}Ac-DOTA-J591 in 32 patients with mCRPC (NCT03276572) [17-19]. This agent displayed hematologic toxicities but were deemed acceptable, even at the highest level of dose (93.3 kBq/kg). In terms of antitumor efficacy, a confirmed 50% decline in prostate specific antigen (PSA) levels (PSA50) was observed in 11 patients (34.4%), with receipt of RP2D (93.3 kBq/kg) as the only dose associated with PSA response (odds ratio, 2.89; P = .3). This antitumor response can be seen in a PSMA positron emission tomography (PET) scan in **Figure 1** [20]. Additionally, the median progression free survival (PFS) was 5.6 months (95% CI, 3.7 to 7.9), and the median overall survival (OS) was 10.7 months (95% CI, 6.5 to 17.2). Overall, ^{225}Ac-J591 has shown acceptable toxicity and moderate tumor response, but follow-up studies are needed to optimize the dose. To explore this, there is currently a phase I/II trial focused on multiple and fractionated dosing of ^{225}Ac-J591 (NCT04506567). There are also several other trials underway utilizing ^{225}Ac-J591 that are investigating the feasibility and safety of retreatment with ^{225}Ac-J591 (NCT04576871), as well as combination therapies of ^{225}Ac-J591 with anti-PD1 therapy and an AR signaling inhibitor (NCT04946370), and ^{225}Ac-J591 with ^{177}Lu-PSMA I&T (NCT04886986).

Another PSMA-directed α-RIT is Bayer's thorium-227 conjugate (PSMA-TTC or BAY 2315497) [21]. This agent showed strong dose-dependent anti-tumor responses in various prostate cancer xenograft models including four

Table 2. Preclinical and clinical studies using α-RIT agents along with their targets and their primary outcomes

Clinical status	Target	Agent(s)	Application	Status	Primary Outcome(s)	Primary Outcome Results
Preclinical	VE-cadherin	^{225}Ac-E4G10	Glioblastoma	Not Applicable	Not Applicable	Not Applicable
Preclinical	CD46	^{225}Ac-DOTA-YS5	mCRPC	Not Applicable	Not Applicable	Not Applicable
Preclinical	CD46	^{212}Pb-TCMC-YS5	mCRPC	Not Applicable	Not Applicable	Not Applicable
Preclinical	CD46	^{225}Ac-Macropa-PEG4-YS5	mCRPC	Not Applicable	Not Applicable	Not Applicable
Preclinical	PSA	^{225}Ac-hu5A10	mCRPC	Not Applicable	Not Applicable	Not Applicable
Preclinical	CD46	^{225}Ac-DOTA-YS5	MM	Not Applicable	Not Applicable	Not Applicable
Phase I	Tenascin	^{211}At-ch81C6	GBM, AA, AO	Completed	Maximum Tolerated Dose (MTD)	MTD not reached
Phase I	PSMA	^{225}Ac-DOTA-J591	mCRPC	Completed	Incidence of Dose-Limiting Toxicities (DLTs) and MTD	MTD not reached, only 1 of 16 patients experienced DLT at 93 kBq/kg
Phase I	PSMA	^{225}Ac-DOTA-J591	mCRPC	Active, not recruiting	DLTs and MTD	Not Applicable (Trial ongoing)
Phase I	PSMA	PSMA-TTC (BAY 2315497)	mCRPC	Completed, not published	DLTs and MTD	Not published
Phase I	hK2	^{225}Ac-DOTA-h11B6 (JNJ-69086420)	mCRPC	Completed	Incidence of Treatment Emergent Adverse Events (TEAEs) and DLTs	Of 57 patients receiving a median cumulative 18.3 (5.4-33.7) MBq, 35/57 experienced ≥3 TEAEs and 9 experienced DLTs
Phase I	CD33	^{225}Ac-Lintuzumab	R/R AML	Completed	MTD and safety profile	MTD was 111 kB/q/kg; DLT was myelosuppression.
Phase I	CD33	^{225}Ac-Lintuzumab with CLAG-M therapy	R/R AML	Completed	MTD, Recommended Phase 2 Dose (RP2D), safety profile, and overall survival (OS)	MTD and R2PD were 27.75 kBq/kg; common 3/4 TEAE were febrile neturopenia (17/26) and leukopenia (13/26), 2-year OS was 23.1%
Phase I	CD33	^{225}Ac-Lintuzumab with venetoclax	R/R AML	Recruiting	Number of participants with DLTs	Not Applicable (Trial ongoing)
Phase I	CD33	^{213}Bi-Lintuzumab	R/R AML	Completed	MTD and toxicity profile	MTD was not reached (>37 MBq/kg); Only grade 3/4 TEAE was reversible myelosuppression (13/17)
Phase I	CD22	^{227}Th-Epratuzumab (BAY 1862864)	R/R NHL	Completed	MTD	MTD was not reached (>6.1 MBq)
Phase I	IGF-1R	^{225}Ac-FPI-1434	IGF-1R positive solid tumors	Recruiting	Incidence of DLTs, Objective response rate (ORR) by RECIST 1.1	Not Applicable (Trial ongoing)
Phase I	MCSP	^{213}Bi-cDTPA-9.2.27	metastatic melanoma	Completed	MTD and safety profile	MTD was not reached (>925 MBq) and no adverse events of any level were observed
Phase I	EGFR	^{213}Bi-anti-EGFR mAb	CIS of the bladder	Completed	Feasibility and safety profile	Feasible and no adverse effects were observed
Phase I	HER2	^{212}Pb-TCMC-trastuzumab	HER2-positive peritoneal metastases	Completed	Safety profile	Up to 27 MBq/m was tolerated with early TEAEs being mild, transient and not dose dependent
Phase I	HER2	^{227}Th-trastuzumab (BAY 2701439)	HER2-positive solid tumors	Completed, not published	Incidence of TEAEs and DLTs, ORR by RECIST 1.1	Not published
Phase I	CEA	^{225}Ac-DOTA-M5A	CEA-positive metastatic solid tumors	Recruiting	MTD, incidence of TEAEs	Not Applicable (Trial ongoing)
Phase I	CD38	^{211}At-OKT-B10 with fludarabine	R/R MM	Not yet recruiting	MTD of ^{211}At-OKT10-B10	Not Applicable (Trial has not started)
Phase I	CD38	^{225}Ac-DOTA-daratumumab with daratumumab	R/R MM	Recruiting	MTD and incidence of DLTs	Not Applicable (Trial ongoing)
Phase I/II	PSMA	^{225}Ac-DOTA-J591	mCRPC	Active, not recruiting	MTD, RP2D, incidence of DLTs, PSA response rate (≥50% decline)	Not Applicable (Trial ongoing)

Phase I/II	PSMA	^{225}Ac-DOTA-J591 with anti-PD1 therapy and AR signaling inhibitor	mCRPC	Recruiting	Incidence of DLTs, RP2D, composite response rate	Not Applicable (Trial ongoing)
Phase I/II	PSMA	^{225}Ac-DOTA-J591 with ^{177}Lu-PSMA I&T	mCRPC	Suspended	MTD, RP2D, incidence of DLTs, PSA response rate (≥50% decline)	Not Applicable (Trial suspended)
Phase I/II	CD33	^{213}Bi-Lintuzumab following cytarabine	R/R AML	Completed	MTD and antileukemic effects	MTD was 37 MBq/kg; Limited grade 3/4 extramedullary toxicities, but 2/21 treatment related deaths. Significant reduction in blasts seen at all dose levels
Phase I/II	CD45	^{211}At-BC8-B10	Hematopoietic stem cell transplant regimen for non-malignant hematologic diseases	Recruiting	Incidence of graft rejection	Not Applicable (Trial ongoing)
Phase I/II	CD45	^{211}At-BC8-B10	Hematopoietic stem cell transplant regimen for malignant hematologic diseases	Recruiting	MTD	Not Applicable (Trial ongoing)

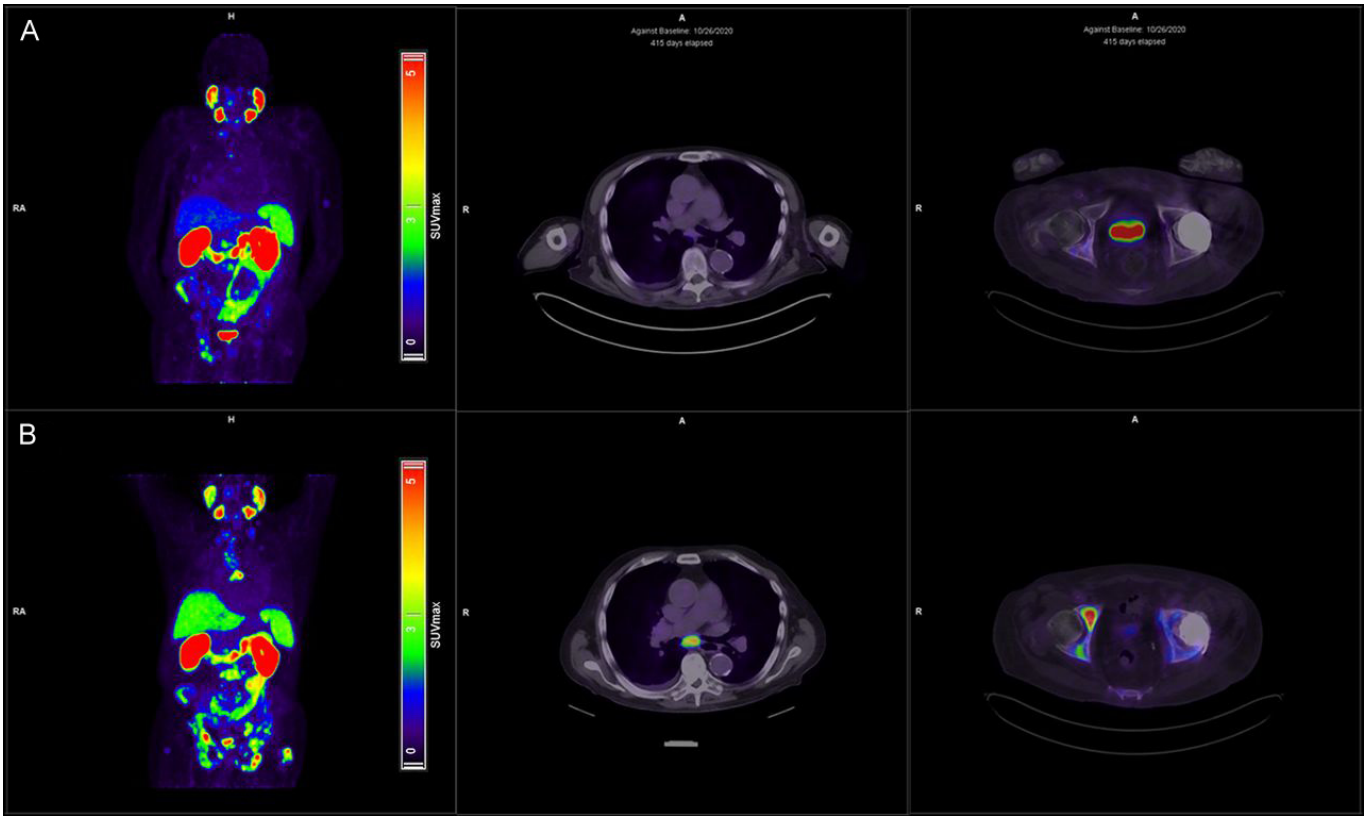


Figure 1. PSMA PET imaging before (B) and after (A) 2 sessions of 225Ac-DOTA-J591 in a patient with metastatic castration-resistant prostate cancer. Post-treatment maximum-intensity-projection images show considerable decrease in disease burden, especially in subcarinal lymph node (column 2) and osseous lesions (column 3) (adapted from literature [20]).

cell-line derived (LNCaP, MDA-PCa-2b, 22Rv1, C4-2) and three patient-derived (ST1273, KUCaP-1 and LuCaP 86.2). Dose-dependent myelosuppression of was observed in some of the models but exhibited signs of recovery. Still, results suggest that PSMA-TTC is generally well tolerated. Due to the efficacy and tolerability of PSMA-TTC in multiple prostate cancer models mimicking various stages of disease progression, clinical development is underway with a phase I trial awaiting results (NCT03724747).

The only other agent treating mCRPC in clinical development is JNJ-69086420, a first-in-class ^{225}Ac-labeled antibody targeting human kallikrein 2 (hK2, *KLK2*). hK2 is a serine protease expressed only in prostate tissue, making it an attractive target for prostate cancer therapy [22]. A dose escalation study to determine the recommended phase 2 dose (RP2D) is underway (NCT04644770). 57 patients were given doses between 5.55 and 14.8 MBq every 8-12 weeks. Preliminary results show some efficacy with high toxicity, 15.8% of patients had to discontinue due to treatment related adverse events (TRAEs), with 4 TRAEs resulting in death. In terms of efficacy, PSA50 and PSA90 rates were 45.6% and 14%, respectively. 6 months after the start of treatment, 28% of patients experienced radiographic progression free survival. RP2D has yet to be determined, and evaluation is ongoing.

There are also several agents currently in preclinical development. PSA is the most common biomarker for prostate cancer screening and is a kallikrein-related serine peptidase [23]. Hu5A10 is a humanized IgG_1-mAb designed to bind free PSA (fPSA) and be internalized into target cells while labeled with ^{225}Ac. In a therapy study using LNCaP-AR xenografts, [^{225}Ac]hu5A10 was compared to beta-emitting [^{90}Y]hu5A10. [^{90}Y]hu5A10 showed more immediate effects on tumor volume, but these effects were not sustained as the median survival time was 188 days for [^{225}Ac]hu5A10, which is significantly longer than the 64 days for [^{90}Y]hu5A10 ($P = 0.0009$). What's more, 7 of 18 mice in the [^{225}Ac]hu5A10-treated group exhibited an unpalpable tumor burden, showing complete responses, compared to just 1 of 9 animals in the [^{90}Y]hu5A10 group.

Another agent in preclinical investigation is CD46-targeting YS5. CD46 is a cell surface antigen that is homogenously expressed in small cell neuroendocrine and adenocarcinoma subtypes [24]. It is therefore overexpressed in both PSMA-negative and PSMA-positive patients, making it an attractive target for treating metastatic prostate cancer. YS5 was first labeled with ^{89}Zr, and demonstrated prostate cancer detection *in vivo*, leading to a first-in-human study for PET imaging purposes (NCT05245006). YS5 has also been radiolabeled with a

^{225}Ac using DOTA as a chelator (^{225}Ac-DOTA-YS5) and significantly inhibited tumor growth when tested in various cell-derived (DU145, 22Rv1) and patient-derived (LTL484, LTL-545) prostate cancer xenograft models. However, 22Rv1-bearing mice treated with a single 18.5 kBq dose exhibited gradual decrease in body weights over the study period, which is consistent with a previous toxicity study. Three fractions of 4.625 kBq were much better tolerated.

Using TCMC (1,4,7,10-tetraaza-1,4,7,10-tetra-(2-carbamoyl methyl)-cyclododecane) as a chelator, the same group conjugated ^{212}Pb to YS5 (^{212}Pb-TCMC-YS5) to test for therapeutic efficacy and tolerability in small animal prostate cancer models [25]. In mice, after a dose escalation study to determine the optimum dose (0.74 MBq), therapy studies were initiated in multiple models such as a subcutaneous mCRPC CDX model (PC3 subcu-CDX), an intraprostate orthotopic mCRPC CDX model (PC3 orthoCDX), and a subcutaneous prostate cancer PDX model. In each tumor model, treated mice demonstrated significant tumor growth inhibition and dramatically increased survival times compared to control groups (saline and cold YS5). The mice in all treatment groups across therapy studies showed steady body weight for the duration of the study. These studies exhibited great preclinical promise for CD46 targeted α-RIT, but clinical translation of this agent has yet to be seen.

Interestingly, while ^{225}Ac-DOTA-YS5 has been mostly investigated in the treatment of mCRPC, its utility in treating multiple myeloma is under preclinical investigation. In patients with a chromosome 1q copy gain, a high-risk subtype of multiple myeloma (MM), CD46 is expressed at a much higher rate in MM cells [26]. Orthometastatic MM xenograft models were treated with three fractions of 4.625 kBq of ^{225}Ac-DOTA-YS5 and 2/7 had no detectable tumor by either bioluminescent imaging or 89Zr-DFO-YS5 PET/CT. Additionally, histological analysis of tissues from these four mice showed no detectable damage to the kidneys, bone marrow, spleen, liver or heart. This study shows the significant therapeutic potential of a fractionated dose of ^{225}Ac-DOTA-YS5 for the treatment of multiple myeloma.

α-RIT's application to mCRPC covers a wide range of targets, with PSMA as the most clinically established. Clinically and preclinically, agents such as ^{225}Ac-DOTA-J591 and ^{227}Th-PSMA-TTC have respectively demonstrated acceptable hematologic toxicities and moderate antitumor activity. hK2 is also exceptionally specific to prostatic cells, but despite promising PSA responses, early clinical data with hK2-targeting ^{225}Ac-JNJ-69086420 has shown a narrow therapeutic window with high hematologic toxicities and several treatment-related deaths. Alternatively, CD46 is a newer, more broadly expressed target that is present on both PSMA-positive and PSMA-negative variants of mCRPC. Preclinical data for ^{225}Ac-DOTA-YS5 and ^{212}Pb-TCMC-YS5 has shown powerful tumor control with improved tolerability with fractionated dosing. Pending clinical translation, CD46-targeted agents hold promise for broader applicability in the treatment of mCRPC. However, for now, PSMA-targeted therapies most favorably balance efficacy and safety in patients while hK2-targeting offers a highly specific but potentially more toxic approach that needs more careful optimization. We await the results of many more clinical trials to further uncover challenges and progress of α-RIT in this context.

Treatment of other solid cancers

α-RIT has also been used to treat a variety of difficult-to-treat solid cancers. For instance, type I insulin-like growth factor receptor (IGF-1R) is overexpressed in several solid malignancies such as sarcomas, pancreatic, breast, ovarian, colon and prostate cancer [27]. FPI-1434 is a ^{225}Ac labeled anti-IGF-1R humanized mAb that is being developed by Fusion pharmaceuticals. While they have published limited data, they report that a single dose of 1.85 kBq of FPI-1434 suppressed tumor growth, while 7.4 and 14.8 kBq caused durable tumor regression in colo-205 xenograft bearing mice [27]. They also report efficacy of single doses in LNCaP and A549 tumor models. Because of this preclinical success, a phase I dose escalation study is underway (NCT03746431) [28].

The mAb 9.2.27, that targets melanoma-associated chondroitin sulfate proteoglycan (MCSP) has been investigated in the treatment of stage IV metastatic melanoma [29]. Expression of MCSP has been shown to increase malignancy of melanoma and anti-MCSP antibody 9.2.27 selectively localizes in melanomas that express the proteoglycan. This antibody was tagged with ^{213}Bi and, after preclinical promise, administered to 38 patients with stage IV metastatic melanoma in a phase I dose escalation study [30]. Doses up to 925 MBq were administered and while MTD was not achieved due to no adverse events of any type, an objective partial response rate of 10% was observed. Median survival was 8.9 months and 40% experienced stable disease at 8 weeks according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. While this α-RIT has demonstrated excellent safety, further dosing may be required to achieve improved therapeutic effects.

α-RIT may also be a preservative treatment option for patients with carcinoma in situ (CIS) of the bladder refractory to bacillus Calmette-Guérin (BCG) treatment [31]. In a pilot study, twelve patients were treated with a single intravesical installation of an anti-epidermal growth factor receptor (EGFR) mAb tagged with ^{213}Bi. No adverse effects were observed at any dose level (366-821 MBq), and three of the 12 patients had no signs of CIS 3, 30, and 44 months after treatment. Due to the safety and potential efficacy, improved treatment may be seen with increased dosage or multiple instillations.

Gliomas are notoriously difficult-to-treat, leading to some of the poorest prognoses among all cancers. There are

many β-RIT in clinical development, but the only reported α-RIT clinical trial addressing gliomas targets tenascin, an extracellular matrix glycoprotein that has elevated expression in gliomas, especially those of high grade [7]. The antibody ch81C6 targets tenascin and after being tagged with 71-347 MBq of ^{211}At, was administered to 18 recurrent high-grade glioma patients in a phase I clinical trial (NCT00003461) [32]. The dose was injected into a surgically created resection cavity (SCRC). No toxicities grade 3 or higher were attributed to the treatment and median survival of all patients was 11.97 months. Another glioblastoma-targeting α-RIT agent, ^{225}Ac-E4G10, displayed the ability to prolong survival time in a clinically relevant mouse model, but this study was completed in 2016, with no follow-up studies published [33]. Additionally, the ch81C6 clinical trial was completed in 2007, and with no follow-up trials in progress, it suggests that α-RIT's progress in this application is much slower compared to others, although this could be due to the resistive nature of gliomas.

Human epidermal growth factor receptor 2 (HER2) is a receptor tyrosine kinase that is overexpressed most commonly in breast cancer but also in cancers like gastric, gastroesophageal, ovary, and bladder among others [34]. Bayer labeled Trastuzumab, a HER2-targeted antibody, with ^{227}Th (BAY2701439, HER2-TTC) and tested this agent in a phase I dose-escalation study (NCT04147819) [35]. 15 patients with advanced HER2-expressing tumors were administered doses starting at 1.5 MBq up to 4.5 MBq to determine MTD. However, MTD was not reached as patients were able to receive multiple cycles of treatment with no reported Dose-Limiting Toxicities (DLTs). No patients experienced partial or complete response and only three participants had stable disease.

Similarly, trastuzumab has been labeled with ^{212}Pb and tested in 18 patients with relapsed intra-abdominal HER2-positive peritoneal metastases (NCT01384253) [36]. In this phase I trial, patients were injected intraperitoneally with 7.4-27.5 MBq/m^2 of ^{212}Pb-TCMC-trastuzumab. All dose levels were well-tolerated with early TRAEs transient and not dose dependent. Additionally, dose-dependent tumor growth inhibition was observed. Overall, α emitter-labeled trastuzumab has displayed safety, but it requires more dosing studies to evaluate its efficacy.

Yet another potential α-RIT application is in the treatment of advanced colorectal cancers that are carcinoembryonic antigen (CEA) positive [37]. For example, ^{225}Ac-OTA-M5A, a CEA-targeting antibody, is being tested in a phase I study that is almost complete (NCT05204147).

α-RIT agents have reached clinical trials in a wide variety of difficult-to-treat solid cancers. Safety and early efficacy have been exhibited in many of these agents, but dosing optimization is required for α-RIT to reach its potential in most, if not all, these applications.

Current challenges and limitations

As seen in almost all α-RIT agents, bone marrow toxicity is the most common adverse effect. For example, JNJ-69086420, the hK2 targeting agent, caused 61.4% of patients to experience Grade 3 or higher treatment-emergent adverse events (TEAEs), most of which were hematologic [22]. This is likely due to the long circulating half-life of antibodies and the radiosensitive nature of the bone marrow, which should not receive more than 150 cGy [10]. Additionally, the fragment crystallizable (Fc) region of a whole antibody may interact with Fc-receptors in myeloid cells [38]. While many agents in this review did not cause intolerable myelosuppression at the doses used, the effects of neutropenia, anemia and thrombocytopenia can cause increased risk of infection, fatigue and bleeding risk, respectively, all of which can negatively impact quality of life for patients [39]. Therefore, decreasing the risk of this toxicity is an important step in the development of α-RIT.

This myelosuppression is often a delayed effect of the therapy, which can make defining MTD in dose-escalation studies with α-RIT challenging. Patients may not exhibit substantial leukopenia at first, which may lead to the next set of patients receiving an inappropriately higher dose. This can be especially challenging to evaluate in fractionated dosing strategies where a previous fraction may confound the toxicity evaluation of a later fraction. In addition to this delayed effect, dose-limiting myelosuppression is often defined as prolonged myelosuppression (grade 4 leukopenia lasting >35 days), which require longer windows of monitoring patients [40]. This can significantly prolong this trial design, which increases costs and slows clinical development of α-RIT agents.

In addition to delayed toxicities, there are many other challenges in designing α-RIT clinical trials. Many trials struggle to obtain enough material to complete their studies, especially dose-escalation trials. For example, Jurcic et al. could not complete their dose-escalation phase I trial due to lack of ^{213}Bi availability [13]. ^{213}Bi is less potent and requires higher doses, which may contribute to the challenge of acquiring enough material. Another hurdle in the use ^{213}Bi is that it has a much shorter half-life, which poses issues ensuring that the desired dose is delivered to the patient after it has been synthesized. These hurdles contribute to the increasing use of ^{225}Ac, but this isotope also has major availability challenges due to difficulties in producing large quantities. Currently, the primary source of ^{225}Ac comes from ^{233}U waste, which also has limited availability [41]. Other production methods include the use of cyclotrons and reactors, but generating pure ^{225}Ac has proved difficult. Use of other α-emitting radionuclides is a potential solution, but they come with tradeoffs as well. ^{211}At and ^{212}Pb use is also limited by their production [38]. On the other hand, ^{227}Th can be produced

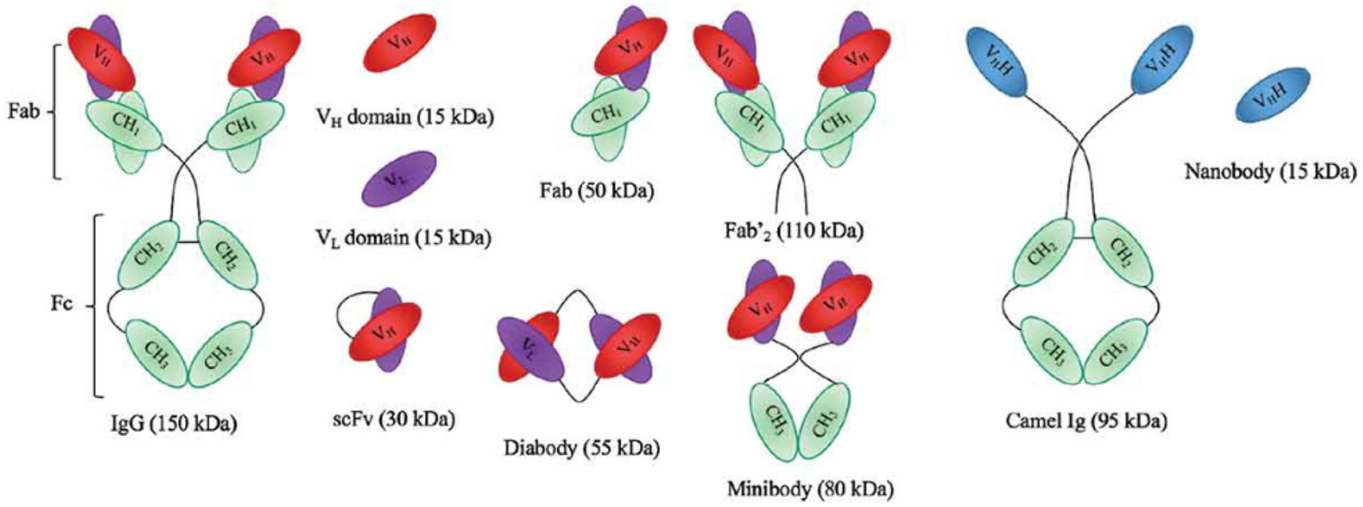


Figure 2. Schematic representation of a conventional mAb and its derived fragments and their corresponding sizes (adapted from the literature [42]).

very easily with current technology, but it delivers fewer α particles and delivers them slower than ^{225}Ac [38, 41].

Another major challenge of using α-emitting radionuclides is the recoil energy that daughter isotopes experience upon α decay [8]. Because this energy is most often at least 100 keV, which is over 1000 times higher than the binding energy of any chemical compound, daughters will release themselves from the targeting ligand and distribute freely in the body, releasing radiation of their own. Most of the time, daughters will be released into the blood stream, and they will preferentially accumulate based on their affinity for certain tissues. For example, ^{221}Fr and ^{213}Bi are daughter isotopes of ^{225}Ac, and they both preferentially accumulate in the kidneys, which can cause renal parenchymal damage, glomerulosclerosis and fibrin thrombi formation [8, 24]. One of the benefits of α-RIT is that antibodies can be internalized by tumor cells, which can prevent the release of daughters into the blood stream, but this effect is dependent on the internalization characteristics of their target [10]. However, at higher doses, circulating unbound antibodies will reintroduce the recoil problem. While the ^{225}Ac labeled α-RIT agents in clinical trials have not reported major kidney toxicity, as dosing studies continue, the distribution of recoiling daughters is an important consideration.

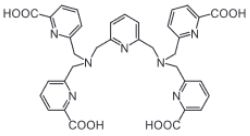
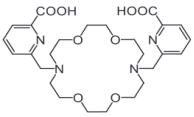
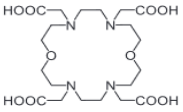
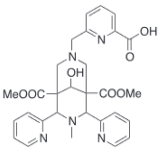
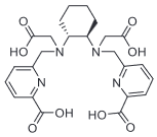
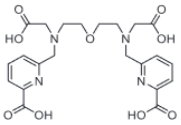
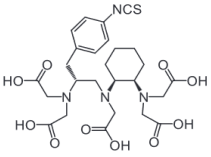
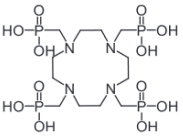
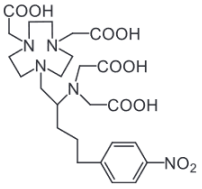
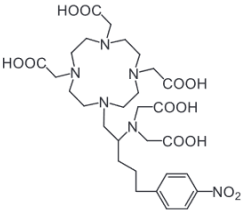
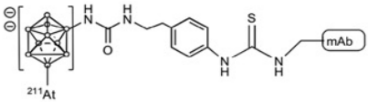
There are also major challenges in the dosimetric assessment of α-RIT agents, partly due to having to factor in the recoil effect and daughter isotopes, which can be difficult. Additionally, there is a gap in calculating dosimetry using imaging. While cameras to detect α particles are being developed, gamma (γ)-cameras are more widely used in clinical settings, which makes it impossible to detect α irradiation to tumors or organs unless the α-emitter is associated with γ rays as well [3, 42]. While administration of the same doses can be tightly controlled, understanding the distribution of dose in the body for different α-RIT agents remains a challenge until α-cameras are more widely available.

In addition to myelosuppression, liver toxicity is a concern when using whole antibodies due to the long circulating half-life and the presence of Fc-receptors in hepatic sinusoidal cells [38]. Additionally, in patients undergoing myeloablative therapy to preparation for alloHCT in AML, a particularly important liver toxicity is veno-occlusive disease (VOD), which can be fatal in up to 80% of patients [43]. For example, in patients being treated with ^{225}Ac-lintuzumab for AML, 3 patients (17%) experienced grade 3 or higher liver function abnormalities, but of the two patients who underwent alloHCT, one died of VOD. While VOD is a known risk of alloHCT, due to the presence of leukemia cells and CD33-expressing reticuloendothelial cells in the liver, treatment of ^{225}Ac-lintuzumab may increase the risk of hepatic toxicity [12]. While VOD may be a concern specific to this agent and application, the potential for hepatic toxicities with whole antibodies is an important consideration for all future α-RIT agents.

Technological innovations driving progress

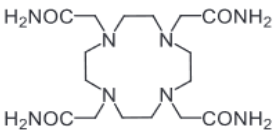
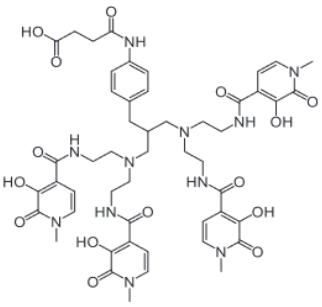
In addition to problems caused by their Fc regions binding to receptors on hepatic sinusoidal and myeloid cells, whole antibodies can struggle to penetrate solid tumors due to their size [10]. Therefore, engineering smaller antibody fragments that lack an Fc region presents a potential solution. Structures and sizes of such fragments are shown in **Figure 2**. Smaller fragments have shown to be delivered more quickly to the tumor, penetrate better and clear from circulation faster [38]. These structures are being tested mostly preclinically, with one example in clinical trials. ^{211}At-MX35-F(ab')$_2$ lacks an Fc region and has shown to achieve therapeutic absorbed doses in tumors without significant toxicity in ovarian cancer patients that

Table 3. Commonly used chelators, their structures, and what radionuclide(s) they coordinate [46]

Radiometal	Ligand Name	Ligand Structure
^{225}Ac, ^{213}Bi, ^{227}Th, ^{212}Pb	DOTA	
^{225}Ac, ^{227}Th	py4pa	
^{225}Ac	macropa	
	crown	
	Bispa[2]	
	CHXoctapa	
	noneunpa	
^{213}Bi	cDPTA, CHX-A"-DTPA	
	DOTP	
	3p-*C*-NETA	
	3p-*C*-DEPA	
^{213}At	B10-NCS	

have been intraperitoneally injected with the fragment (NCT04461457) [44]. A HER2-directed diabody has demonstrated preclinical promise, but the majority of efforts are in the use of nanobodies as a targeting vector [38]. Hurley, et al.'s review of α emitting-tagged nanobodies describes many preclinical studies that demonstrate the efficacy and safety of nanobodies in a variety of potential clinical applications. One concern is the renal accumulation of these smaller fragments, but many of these studies found effective reduction with co-infusion of gelofusine, a plasma expander, and/or lysine [38, 45]. Overall, while there is preclinical promise that this technology can improve the safety of α-RIT, there still needs to be clinical validation of these constructs.

Another area of progress is in the radiolabeling of the targeting vectors. Finding the optimal chelator for each α-emitting radionuclide is critical to ensure they remain stable *in vivo* in order to reduce off-target tissue localization [46]. Commonly used chelators and their structures are shown in **Table 3**. There are a variety of characteristics that comprise an ideal chelator. These include fast complexation kinetics, high selectivity for the radioisotope of interest to minimize impurities, high *in vivo* stability, high thermodynamic stability, and the ability to bind an imaging radionuclide for theranostic purposes [46]. Some agents are already using an optimized chelator for their respective radionuclide. These include ^{211}At-labeled agents that use isothiocyanatophenyl-closo-decaborate (B10) boron cage and ^{212}Pb-labeled agents that use TCMC. B10 provides high labeling efficiency (75%-90% yield, 1 min) of ^{211}At with high in vivo stability, which is why it is currently being used in several clinical trials shown in **Table 2** [47]. In preclinical studies, TCMC proved to be more stable and more efficient in labeling compared to DOTA, which is why many ^{212}Pb-labeled agents in clinical trials use TCMC [48]. Due to the oxophilic nature of ^{227}Th, 4 bidentate 3-hydroxy-N-methyl-2-pyridinones (Me-3,2-HOPO) is the current gold standard for coordinating ^{227}Th because of its oxygen-rich structure and it is therefore currently used in clinical trials. However, chemical synthesis is challeng-

^{212}Pb	TCMC	
^{227}Th	Me-3,2-HOPO	

Abbreviations: DOTA,1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; cDTPA/CHX-A"-DTPA, (S,S)-cyclohexane-1,2-diaminepentaacetic acid; DOTP, 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic acid); NETA, {4-[2(bis-carboxymethyl-amino)-ethyl]-7-carboxymethyl-[1,4,7]triazonan-1-yl}-acetic acid; DEPA, 7-[2-(bis-carboxymethyl-amino)-ethyl]-4,10-bis-carboxymethyl1,4,7, 10-tetraaza-cyclododec-1-yl-acetic acid; B10, isothiocyanatophenyl-*closo*-decaborate(2-); TCMC, 1,4,7,10-tetraaza-1,4,7,10-tetra-(2-carbamoyl methyl)-cyclododecane; Me-3,2-HOPO, 4 bidentate 3-hydroxy-N-methyl-2-pyridinones.

ing with this chelator, so developing more readily accessible polydentate oxygen-rich chelates is necessary for advancing ^{227}Th-based α-RIT.

Chelation moieties for the other commonly used isotopes need to be improved, but there is progress being made. ^{225}Ac is the most used radionuclide and all agents in clinical development use DOTA for chelation. However, macropa, a large macrocyclic chelate, has been shown to coordinate ^{225}Ac at a higher efficiency than DOTA. It was tested along with an addition of a PEG_4 linker to address the significant toxicity of ^{225}Ac-DOTA-YS5 [49]. They found ^{225}Ac-Macropa-PEG_4-YS5 is more stable with higher chelation efficiency compared to ^{225}Ac-DOTA-YS5 and ^{225}Ac-Macropa-PEG_0-YS5. In an *ex-vivo* biodistribution study using the 22Rv1 tumor model, ^{225}Ac-Macropa-PEG_4-YS5 was also found to have higher tumor-to-kidney ratios compared to ^{225}Ac-DOTA-YS5. Both constructs were then assessed for therapeutic potential in 22Rv1 subcutaneous xenografts. Both conjugates significantly increased median survival times compared to the vehicle group, but ^{225}Ac-Macropa-PEG_4-YS5 displayed statistically significant longer median survival time in the lower dose group (0.4625 kBq) compared to ^{225}Ac-DOTA-YS5. Other ^{225}Ac chelators such as crown, py4pa, bispa^2, CHXoctapa and noneunpa have all displayed high labeling yield low lower chelate concentrations [46]. Despite these improvements, only DOTA has been used to chelate ^{225}Ac in clinical settings, but these newer chelators show significant preclinical promise. In terms of ^{213}Bi, so far, the only clinically used chelator has been *p*-SCN-Bn-CHX-A"-DTPA (cDTPA), but it only has 76% stability in human plasma. However, phosphorus-containing cyclen chelator DOTP has demonstrated higher stability in human serum compared to cDTPA. Other novel chelates have been developed such as {4-[2(bis-carboxymethyl-amino)-ethyl]-7-carboxymethyl-[1,4,7]triazonan-1-yl}-acetic acid (NETA) and 7-[2-(bis-carboxymethyl-amino)-ethyl]-4,10-bis-carboxymethyl1,4,7, 10-tetraaza-cyclododec-1-yl-acetic acid (DEPA). Both of these have shown to coordinate $^{205/206}$Bi with high efficiency at low temperatures as well as low kidney uptake and high tumor accumulation when linked to trastuzumab [50, 51]. However, while these chelates have shown significant promise, they have yet to be applied in clinical settings.

Future directions and emerging opportunities

Using α-RIT agents in combination with other treatment regimens is one of the more common and promising applications of this technology. For example, ^{225}Ac-lintuzumab has been tested as a monotherapy and in combination with CLAG-M therapy for the allo-HCT conditioning of R/R AML patients. In a dose escalation phase I trial of the combination therapy, four cohorts of a total of 21 patients received a fixed dose and schedule of CLAG-M and a single infusion of ^{225}Ac-lintuzumab with doses ranging from 9.25 to 37 kBq/kg (NCT03441048) [11]. 27.75 kBq/kg was determined to be the MTD and RP2D and the most common grade 3/4 TEAEs were hematologic, but importantly, no patients had to discontinue study treatment due to adverse events and no significant renal or hepatic toxicities were observed. Also, the overall response rate, which included complete remission, composite complete remission and morphologic leukemia-free state, was 65.2% for all patients, and 75% at RP2D. In the trial that used ^{225}Ac-lintuzumab alone, no remission was seen in any patient, demonstrating the efficacy of combination therapies involving α-RIT [12].

^{213}Bi-lintuzumab was also evaluated following cytoreductive cytarabine treatment in a phase I/II trial in the treatment of AML [40]. Compared to its monotherapy, ^{213}Bi-lintuzumab displayed a much longer median response duration (6 months compared to 19 days) and increased clinical responses (21% ORR compared to 0%) [13, 40]. However, toxicity was a concern as high grade liver function abnormalities were observed in 5 of the 21 enrolled patients, and 2 patients experienced treatment-related deaths. Myelosuppression was also dose limiting, which led to 37 MBq/kg being selected as MTD. Despite the toxicities, this study encourages the sequential administration of cytarabine and ^{213}Bi-lintuzumab in patients with AML and further suggests the efficacy of lintuzumab α-RIT in combination with another cytotoxic chemotherapy. Additionally, there are many combination therapies in

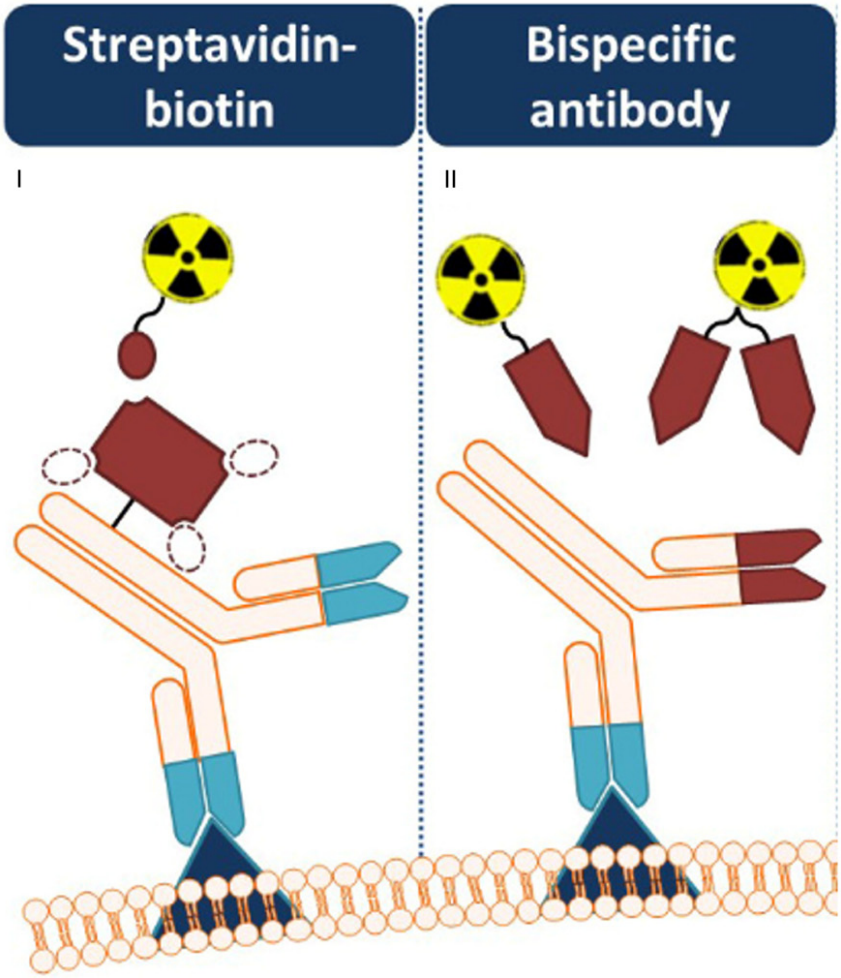


Figure 3. Two common methods of pretargeting. I) The streptavin-biotin strategy with the dotted circles representing potential biotin binding sites on streptavidin. II) The bispecific antibody approach with the left small molecule as a monovalent hapten and the right as a bivalent hapten that has the ability to bridge tow antibodies (adapted from the literature [52]).

clinical trials that are awaiting results. These include ^{225}Ac-lintuzumab with venetoclax in AML patients (NCT03867682), ^{211}At-OKT-B10 with fludarabine in R/R MM patients (NCT04579523), and several ^{225}Ac-DOTA-J591 combinations in the treatment of mCRPC (NCT04576871, NCT04946370).

Another promising future direction of α-RIT is pretargeting. This approach involves injecting a targeting vector, allowing it to accumulate at the target, and then injecting an effector molecule which will bind to the vector *in vivo* [52]. The benefit to this strategy is its ability to widen the therapeutic index by decreasing the dose of off-target irradiation caused by long circulating half-life. This strategy has been heavily studied using β-emitters in both solid and hematologic cancers. In pretargeted radioimmunotherapy (PRIT), the two most common methods are shown in **Figure 3**. In the avidin-biotin system, the targeting antibody is linked to avidin or streptavidin (SA) that has four binding sites for biotin, which is tagged with the radionuclide. This system has demonstrated preclinical and clinical efficacy but has problems with immunogenicity. For example, in a phase I/II study with ^{90}Y-tagged, CD-20 targeted SA-biotin PRIT in relapsed NHL showed pretargeting resulted in superior tumor-to-whole body dose ratios compared to other studies that used conventional RIT [53]. Tumors also regressed in six of the seven patients. However, patients developed immune responses to SA, which limited treatment to one cycle.

To overcome this, the other common PRIT method is using bispecific antibodies (bsAbs) with one arm directed to a tumor antigen and the other to a radiolabeled hapten. There are many preclinical successes with this strategy, but few clinical successes, likely due to the use of murine or chimeric antibodies and the development of human anti-mouse antibody responses. Therefore, fully humanized constructs have been developed and have demonstrated early clinical safety in humans, but these constructs are more complex and costly to produce [52, 54].

While most of the literature has been focused on the use of β-emitters in PRIT, there have been some preclinical studies focused on α-PRIT that show promise. For example, in an AML xenograft model, using ^{213}Bi, anti-CD45 α-PRIT was shown to be 60% more effective than β-PRIT [55]. ^{211}At and ^{225}Ac have also been used in α-PRIT, but nonspecific radioactive uptake in the kidneys has been observed [52]. Strategies to overcome this hurdle are critical for clinical success.

Fractionated dosing is another avenue to widen the therapeutic index that warrants future exploration. This dosing strategy, which uses multiple, usually smaller doses, reduces toxicity, increases tumor dose and prolongs tumor response by permitting treatment over time [56]. In a preclinical study using ^{225}Ac-labeled YS5, fractionated doses have shown to be better tolerated with similar efficacy compared to a single, higher dose when treating mCRPC [24]. Additionally, ^{225}Ac-DOTA-YS5 and ^{225}Ac-Macropa-PEG$_4$-YS5 have exhibited very high efficacy in preclinical models of MM and mCRPC, respectively [26, 49]. Clinically speaking, there is currently a phase I/II trial focused on multiple and fractionated dosing of ^{225}Ac-J591 (NCT04506567). However, it is important to keep in mind that the aforementioned challenges in trial design with α-RIT agents such as toxicity evaluation, isotope availabil-

ity, and dosimetry assessment can be amplified with a complex dosing strategy such as fractionation.

Concluding remarks

In summary, we have reviewed the current landscape of α-RIT agents in their preclinical and clinical development. α-RIT is an emerging area of cancer treatment due to its high energy output and short range, enhancing the potency and specificity of radiotherapeutics. α-RIT agents have been deployed in a wide variety of clinical applications, with the largest focus on mCRPC and relapsed or refractory hematologic cancers. With the preclinical promise of these agents, many of them have been moved into phase I/II clinical trials. In these trials, early efficacy has been displayed with variable safety outcomes. Most studies reported acceptable toxicities; however, hematologic toxicities were consistently observed across all isotopes and agents. Other challenges include off-target toxicity caused by the recoil effect releasing daughters into the blood stream and difficulty optimizing dosing because of hurdles in measuring dosimetry with α-emitters. Strategies to widen the therapeutic window have included fractionated dosing, combination with other therapies, pretargeting, as well as the use of novel chelators and antibody constructs. More studies to further evaluate α-RIT are critical to optimize the use of this technology. There are many clinical trials underway, and we eagerly await their results.

Acknowledgements

This project was funded with support from the Indiana Clinical and Translational Sciences Institute, and in part by UL1TR002529 from the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosure of conflict of interest

None.

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