Review

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Recommendations on the Clinical Application and Future Potential of α-Particle Therapy. A Comprehensive Review of the Results from the SECURE Project

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Review

Recommendations on the Clinical Application and Future Potential of α-Particle Therapy. A Comprehensive Review of the Results from the SECURE Project

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Abstract

Background/Objectives The document comprehensively reviews the clinical applications and future potential of alpha-emitting radionuclides available for targeted alpha-particle therapy (TAT) in cancer treatment. The approval of radium-223 (Ra-223) therapy in 2013 marked a significant advancement in alpha-emitting therapeutic radiopharmaceuticals, which are primarily used in treatment of prostate cancer. The EU SECURE project was introduced as a major initiative to enhance the sustainability and safety of medical alpha-emitting radionuclides production in Europe. **Methods**: This literature review was conducted by a multidisciplinary team on selected radionuclides, including actinium-225, bismuth-213, astatine-211, lead-212, terbium-149, radium-22323 and thorium-227. These were selected based on their clinical significance, as identified in the EU PRISMAP project [1] and subsequent literature searches. The review process involved searching major databases using specific keywords related to alpha-emitter therapy and was limited to articles in English. For each selected radionuclide, the physical characteristics, the radiochemistry, and the pre-clinical and clinical studies are explored. **Results of** the review show current and potential clinical applications of new alpha-emitting radionuclides, sharing insights from the SECURE consortium's experiences and providing recommendations for future clinical trials to establish the therapeutic efficacy of these radionuclides. **Conclusion:** For each selected radionuclide, conclusion are reported in individual chapters. The results highlight the advantages of alpha particles in targeting cancer cells with minimal radiation to normal tissue, emphasising the need for high specificity and stability in delivery mechanisms**,** but also suggest that the full clinical potential of alpha particle therapy remains unexplored. Theranostic approach and dosimetric evaluations still represent relevant challenges.

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1. Introduction

The short range of alpha particles makes them a clear candidate for treating single cancer cells and solid tumours, minimising the levels of unwanted radiation to the normal tissue if one can ensure high specificity and stability in the delivery mechanisms associated with developing appropriate targeting molecules. The approval of radium-223 therapy for clinical use in cancer treatment in 2013 was the starting point for developing alpha-emitting therapeutic radiopharmaceuticals. Current clinical applications have been predominantly focusing on the field of prostate cancer, but the full clinical potential of alpha particle therapy has not been explored yet. Different scenarios will be outlined to define alternative clinical applications. These will include the possibility of using alpha particle therapy as part of second-line therapy in patients with other treatment failures or in combination with other therapies such as external beam radiotherapy or different chemotherapy and/or anti-angiogenic treatment regimens.

Despite the potential use in targeted alpha-particle therapy (TAT), several challenges remain. The main issue is the stability of molecules labeled with an α-particle emitter, which is affected by bond cleavage from kinetic energy post-α-decay (recoil effect), differing coordination chemistry properties of daughter nuclides, and the radiolysis effect.

The recoil energy from the α-decay process generally exceeds 100 keV, significantly higher than any chemical bond's binding energy. As a result, the bond between the α-emitter and the chelating agent, carrier system, or entire bioconjugate is likely to break, releasing radioactive daughters. The coordination characteristics of a radionuclide can differ significantly from those of its decay products, which may lead to chemical instability in the metal-chelator complexes. Additionally, for radionuclides with complex decay chains such as actinium-225 (Ac-225), thorium-227 (Th-227) and lead-212 (Pb-212), the variations in the coordination chemistry between parent and daughter isotopes become critical. This is because a single chelating agent is generally insufficient to bind all the daughter effective isotopes throughout the decay chain. The recoil effect and changes in coordination are crucial when daughter radionuclides are α-emitters, as they may accumulate in off-target areas and deposit cytotoxic energy at undesired locations if they reach their biological target. Finding new chelators is crucial for translating α-particle emitters from research to clinical use. Radiolysis from high LET α-particles and reactive radicals can degrade radiopharmaceuticals during production and storage.

All these scenarios will be considered within the context of different clinical cancer models, including glioblastoma, neuroendocrine tumors, bone metastases, multiple myeloma, and associated standard state-of-the-art treatment techniques.

The EU SECURE project (Strengthening the European Chain of sUpply for next generation medical RadionuclidEs) aims to contribute to the sustainability of medical isotope production and its safe application in Europe. It focuses on promising developments in the design of irradiation targets and production routes for existing and new isotopes in nuclear therapy and diagnostics. The multidisciplinary SECURE consortium aims to identify and efficiently utilise current resources for new radionuclides, especially alpha emitters and beta-emitting theragnostic radionuclides, creating opportunities in society, healthcare, and economics.

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2. Results

2.1. Actinium-225

2.1.1. Physical Characteristics

Actinium is a radioactive component with atomic number 89 [1]. Only two of its 32 isotopes, actinium-228 (Ac-228) and actinium-227 (Ac-227), are naturally produced by the disintegration of thorium-232 (Th-232) and uranium-235 (U-235), respectively [1,2]. With its long half-life of 21.7 years and predominant β-emission decay, Ac-227 represents the most common actinium isotope. However, Ac-228, a β-emitter, is highly uncommon [1,2].

Actinium-225 is the initial element in the actinide family, and its radioactive parents are parts of the now-extinct "neptunium series" [1,3]. This alpha emitter isotope has a long half-life of 9.9 days [4,5].

From Ac-225 to Bi-209 (T1/2 = 1.9×10^{19} y), the decay series includes six short-lived radionuclide daughters [4,6]. This radioactive cascade is represented by francium-221 (T1/2 = 4.8 min; 6.3 MeV α particle and 218 keV γ emission), astatine-217 (At-217) (T1/2 = 32.3 ms; 7.1 MeV α particle), bismuth-213 (T1/2 = 45.6 min; 5.9 MeV α particle, 492 keV β− particle and 440 keV γ emission), polonium-213 (T1/2 = 3.72 μs; 8.4 MeV α particle), thallium-209 (T1/2 = 2.2 min; 178 keV β− particle), lead-209 (T1/2 = 3.23 h; 198 keV β− particle) and stable bismuth-209 (Figure 1) [7,8].

Actinium-225 is considered a "nanogenerator" since one decay of this element produces four α, three β particles, and two γ emissions [7]. The α particle emissions and the rapid disintegration of Ac-225 make it an appealing choice for targeted radionuclide therapy (TAT) [7,9]. However, it is essential to consider the notable Ac-225 cytotoxicity due to its extended half-life and the various α particles produced throughout its decay chain [4].

Moreover, the potential use of γ disintegrations, produced by the decay of the intermediate francium-221 (218 keV, 11.6% emission probability) and bismuth-213 (440 keV, 26.1% emission probability) [4] in SPECT in vivo imaging, could lead the Ac-225 radioactive cascade to a possible theragnostic perspective and nuclear medicine applications.

However, the recoil effect remains a challenge that must be carefully managed to maximize its potential. Innovations in encapsulation, intracellular delivery, and chelation chemistry are helping to mitigate recoil and enhance the safety and effectiveness of Ac-225 in clinical applications.

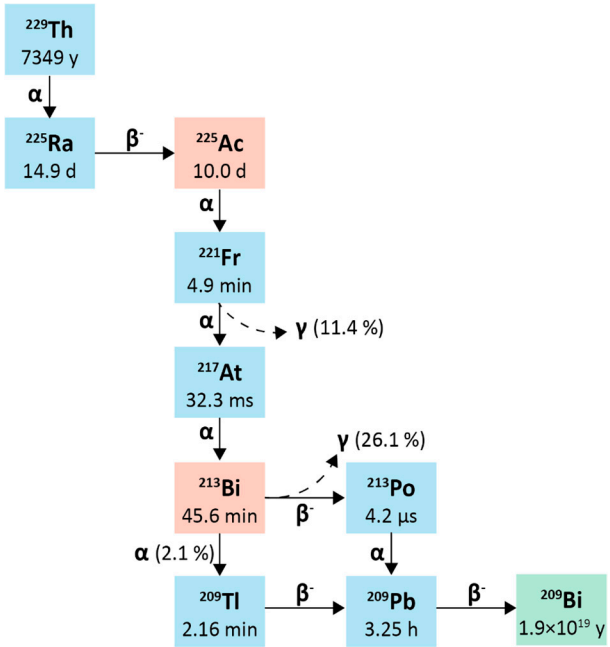

Figure 1. Decay chain of Uranium-233 to Actinium-225 and Bismuth-213.

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Planar SPECT imaging faces challenges due to Ac-225 effectiveness, resulting in low doses and γ emissions. Using Bismuth-213 from Ac-225 decay is a potential solution, but Bismuth-213's short half-life (45.6 min) complicates processing, radiolabelling, and radiopharmaceutical delivery. Monitoring these reactions is also challenging due to the necessary radiation and the requirement of a 6-hour secular equilibrium for accurate radiochemical yield measurement. Actinium's chemistry remains underdeveloped due to limited availability and the specific management needed for all Ac isotopes.

As previously mentioned, Ac-225 is part of the neptunium-237 decay series, which is no longer found naturally. This radioactive element can be artificially synthesized [1]. In addition to direct production methods, Ac-225 can be accessed at several key points along its decay chain, including uranium-233 (half-life = 159,200 years, 100% alpha emission), thorium-229 (half-life = 7,340 years, 100% alpha emission), and radium-225 (half-life = 14.9 days, 100% beta-minus emission) [3].

Actinium-225 has significantly fewer nucleons than other actinide nuclei, making it less stable than production targets such as thorium-232 and radium-226 [3]. Consequently, production methods typically rely on radioactive decay or high-energy bombardments, with few exceptions.

The available production routes of Ac-225 and its parents are listed below.

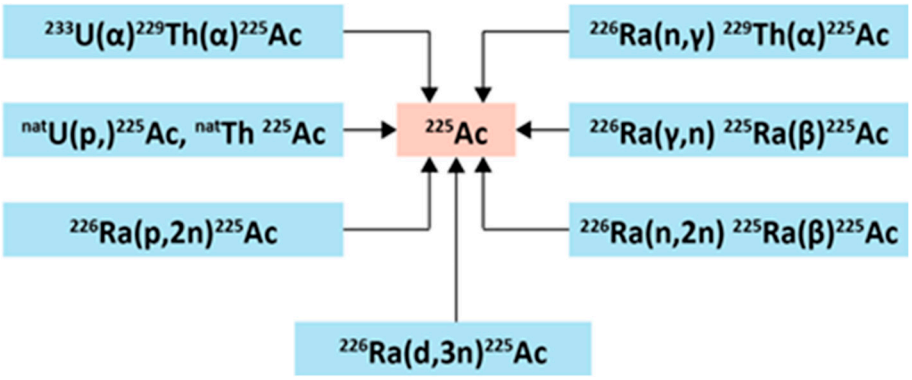

Figure 2. The principal production routes for Ac-225.

2.1.1.1. Radiochemical Extraction from Thorium-229

For over two decades, the primary source of Ac-225 has been the accumulation of thorium-229 (T1/2 =7,340 y) from the disintegration of uranium-233 (T1/2 = 160,000 y) reserves. All clinical trials and many preclinical studies involving Ac-225 and bismuth-213 (Bi-213) have used this generation route [4].

A large portion of uranium-233 was created between 1954 and 1970 by neutron irradiating thorium-232 while it was under research for nuclear weapons and reactors never wholly implemented [10,11]. Nuclear plants have a significant stockpile of uranium-233 after the thorium fuel cycle was abandoned in favour of fast reactors powered by plutonium at the end of the 1970s [1]. From supplies kept at the Oak Ridge National Laboratory (ORNL, Oak Ridge, USA), thorium-229 produced via uranium-233 disintegrations was recovered between 1995 and 2005 [11]. Currently, there are three principal sources for this Thorium-229: at ORNL (5.55 GBq (150 mCi), or 704 mg) [11,12], at the Directorate for Nuclear Safety and Security of the Joint Research Centre (JRC) of the European Commission (JRC, Karlsruhe, Germany) (1.7 (46 mCi), or 215 mg) formerly known as the Institute for Transuranium Elements (ITU) [12,13], and at the Leipunskii Institute for Physics and Power Engineering (IPPE, Obninsk, Russia) (5.55 GBq (150 mCi), 704 mg) [11,14]. The Canadian Nuclear Laboratories has more recently announced the isolation of a crucial Thorium-229 source [4]. Very pure sources of Thorium-229 were also discovered, prepared, and used for preclinical research at the Belgian Nuclear Research Centre (SCK CEN) in Mol, Belgium [15].

By producing approximately 33 GBq (893,23 mCi) (ORNL) [18] and 13.1 GBq (350 mCi) (JRC) [11,13] of Ac-225 annually, ORNL and JRC represent, up to now, the principal worldwide providers

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of Ac-225 and its parent Ram-225 (T1/2 = 14.9 d). Anion exchange and extraction chromatography are combined to produce Ac-225 from Thorium-229 at JRC Karlsruhe, whereas anion and cation exchange are used at ORNL [16]. Even though the IPPE source has the same amount of Thorium-229 as the ORNL source, recorded values show that this source intermittently produces Ac-225 [11,14,17]. According to [20], IPPE Actinium-225 production could reach 22 GBq per year.

Additionally, it has been noted that, beginning in 2019, the extraction of Th-229 from historical waste stored by the US Department of Energy is expected to considerably increase the availability of Th-229 [16]. According to estimations, up to 45 g of the total Th-229 could be available, which could result in a 40-fold boost in the supply of Actinium-225 above current levels [16].

Approximately 68 GBq of Ac-225 from Th-229 are generated annually globally [4]. Knowing that he Ac-225-labelled ligands given activities typically range from 4 to 50 MBq per therapeutic dosage [4], this isotope's supply is sufficient to treat several hundred patients annually and permits the performance of preclinical research. Although a significant benefit of this production method is that the resulting Ac-225 is free of other actinium isotopes, the globally generated Thorium-229 is not enough to satisfy the extensive use and implementation in healthcare applications worldwide [11]. Therefore, the development of Ac-225 radiopharmaceuticals is hindered by the limited supply and high cost that make Ac-225 inaccessible to many researchers [11]. In addition, the production of 233U (T1/2 = 160,000 y) is not viewed as a realistic solution for addressing expected short-term Ac-225 demand because decades of steady growth are necessary to boost Th-229 (T1/2 =7,340 y) supply, consequently [3,18,19]. As a result, numerous other techniques for generating Ac-225 on a wide scale have been researched.

Exposing radium targets to high fluxes of thermal neutrons is considered an effective procedure to induce Th-229 production [3]. ORNL researchers have carefully investigated this approach with access to the High Flux Isotope Reactor's (HRIF) >1015 n cm-2 s-1 thermal flux, noticing the production of Th-229 from Ra-226, Ra-228, and Ac-227 [5]. A HFIR cycle of 26 day generated thorium-229 yields at 74 ± 7.4 MBq/g from Ra-226, 260 ± 10 Bq/g Th-229 from Ra-228, and 1200 ± 50 MBq/g from Ac-227 [3,20].

The predominant generation pathway from Radium-226 targets, ^{226}Ra(n,γ), ^{227}Ra(β-) ^{227}Ac (n,γ) ^{228}Ac (β-) ^{228}Th (n,γ) ^{229}Th, is driven by a combination of neutron capture probability and decay kinetics [3]. The short half-lives of Ra-227 (T1/2 = 42.2 min, 100% β-) and Ac-238 (T1/2 = 6.15 h, 100% β-) represented the crucial restrictions for these possible Thorium-229 generation routes [3]. The magnitude of the ^{226}Ra(n, γ) ^{229}Th cross-section has the most significant impact on the amount of Th-229 that can be produced [3]. Unfortunately, this predominant pathway passes through Th-228. This thorium radionuclide is a dosimetrically undesirable contaminant that can only be eliminated from Thorium-229 by mass isolation or burnup, and lowers the yield of Th-229 that may be produced [3]. Handling the radium target and generating Th-228 (T1/2 = 1.9 y) represent essential challenges of this process [8,21]. In addition, there is still a sizable gap between theoretically predicted and measured yields. In HFIR, ideal 5-cycle activations are expected to provide approximately 0.8 GBq (20 mCi g-1) of Th-229 for every gram of Ra-226 [3].

Whereas pure Ac-227 or Ra-228 targets are projected to generate somewhat more Thorium-229, the current supply of these radionuclides is substantially less than that of Ra-226 [3].

2.1.1.2. Accelerator-Based Routes

2.1.1.2.1. The Spallation of Thorium-232

This method is based on the spallation of Th-232 to produce Ac-225. As a target material, Th-232 (4.1103 Bq/g, 110 nCi/g) is widely accessible, not excessively radioactive, and presents fewer radiation risks [11,22]. Due to its accessibility, recycling Th-232 target material may not be an issue.

The irradiation of Th-232 with highly energetic protons (0.6–2 GeV) accessible at large accelerators has produced considerable amounts of Ac-225 [4,23,24]. Production yields of several GBq have been recorded for 10 days' irradiations utilising highly energetic proton beams [5,25,26]. From

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the irradiations of 5 g cm^{-2} targets throughout their roughly 8-month annual running durations, Los Alamos National Laboratory can create between 40 and 80 GBq (1-2 Ci) every 10 days. Once the targets are being handled and the completed product is delivered from ORNL, irradiations can be carried out at Brookhaven National Laboratory (200 MeV at 165 mA) and Los Alamos National Laboratory (100 MeV at 275 mA) [16].

The co-production of long-lived Ac-227 (T1/2 = 21.8 years) is the process's primary constraint [4,27–29].

The effects of the isotopic impurity on the therapeutic application of the produced Ac-225 need to be considered because Ac-225 and Ac-227 cannot be chemically separated (0.1–0.2% of the relative activity of Ac-225) [1,24]. Even with this limitation, Ac-225 produced from high-energy accelerators may still be perfectly suitable for manufacturing Ac-225 /Bi-213 generators, as all actinium daughters will be kept on the generator [8].

According to preliminary research, the Ac-227 impurity will not significantly affect patient dosimetry [18]. Recently, new purifying techniques have been developed that enable a reduction in the Ac-227 level and the recovery of Ac-225 with better purity, such as isotope separation (Isotope Separation On-Line, ISOL at TRIUMF) or a manufacturing method using radium-225 produced after proton irradiation of thorium-232 [1,30,31].

Nonetheless, challenges remain regarding long-lived Ac-227 licensing and accessibility in medical applications. In addition, with a half-life of 21.8 years, waste management is still a serious issue that will necessitate measures with possibly high related costs.

2.1.1.2.2. Proton Irradiation of Radium-226

Compared to the Th-232 spallation reaction, the generation of Ac-225 from Ra-226 targets by proton irradiation in a cyclotron in the Ra-226(p,2n) Act-225 nuclear reaction has several benefits. In medium-sized cyclotrons, at proton energies below 20 MeV (around 16 MeV), this procedure can be carried out 500 patient doses of 10 MBq Ac-225, should be produced after 24-hour exposure to 50 mg Ra-226 to the highest excitation function at 15–16 MeV with a current of 100 mA protons [15,16,32,33].

Since no other long-lived actinium isotopes, such as Ac-227, are created, Ac-225 with high isotopic purity is obtained. By choosing the correct proton energies, it is possible to reduce the co-production of the short-lived actinium-226 (T1/2 = 29 hours) and Ac-224 (T1/2 = 2.9 hours) impurities produced by the reactions Ra-226 (p,n) Ac-226 and Ra-226 (p,3n) Ac-224 [4,16]. Furthermore, during the time needed for target cooling and reprocessing, their activity will continue to decrease to low levels. The production, processing, and control of targets containing milligram quantities of radioactive Ra-226 (T1/2 = 1600 years), as well as the control of its highly radiotoxic gaseous decay product radon-222 (T1/2 = 3.8 days) [4,8,33,34] pose the procedure's principal difficulties [4,16]. In addition, due to the limited availability of the target material, it is necessary to consider its recycling process [2].

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2.1.1.2.4. Deuterons Irradiation of Radium-226

Producing Ac-225 has been proposed by irradiating Ra-226 with deuterons through the reaction Ra-226(d,3n) Ac-225 [35]. Although experimental measurements of the reaction's cross-sections are still in development, simulations indicate that the process will have a bit greater production yield than the Ra-226(p,2n) Ac-225 reaction and a maximum cross-section of 864 mb at 18.5 MeV [16].

Since deuteron irradiation might result in an increased co-production of actinium-226 (T1/2 = 29 hours), a prolonged cooling time should be considered to allow the actinium-226 decay [16]. This factor is a critical consideration in the production process and must be carefully managed to ensure the quality of the final product.

2.1.1.2.5. Photonuclear Irradiation of Radium-226

The photonuclear reaction Ra-226(γ,n) Ra-225, followed by the beta decay of Ra-225 to Ac-225, is a different method for producing Ac-225 by irradiating Ra-226. It was noticed that the photon energy cut-off for the reaction was 6.4 MeV. However, experimentally established cross-section data are not yet available [16]. A zircaloy capsule containing 1 mg of Ra-226 embedded in an 800 mg of BaCl2 matrix underwent 3.5 hours of 52 MeV betatron irradiation to generate 0.24 mCi of Ac-225 [16]. At a maximum photon energy of 24 MeV, a radiation yield of 550 Bq/(mAh mg radium-226) was recorded [36]. For a more precise estimate of production yields, it is essential to quantify the cross-section data in detail for this reaction.

The Ra-226 target recycling requirement and issues with the radon-222 emission represent the principal difficulties regarding this approach [2]. However, large-scale Ac-225 manufacturing using this procedure is already being implemented at several plants [37,38].

SCK-CEN and IBA inked a research and development partnership agreement named Pantera for the joint production of Ac-225 in 2021. Thorium-229 naturally decays to Ra-225 and then Ac-225, which allows for extracting significant amounts of Ac-225. This generator will be installed in a Pantera production facility hosted on the premises of SCK CEN (EU H2020 project PANTERA -PAN European Technology Energy Research Approach).

2.1.2. Radiochemistry

Actinium typically exists as a +3 ion in water, with chemical properties similar to lanthanum +3. La3+ is often used as a nonradioactive surrogate for Ac3+. The 6-coordinate ionic radius of La3+ (1.03 Å) is smaller than Ac3+ (1.12 Å) [39]. The low charge density renders Ac3+ a very basic +3 ion. The first hydrolysis constant, pK1h, represents the ability of the metal to polarise coordinated water to favour the release of a proton and the formation of AcOH2+. For Ac3+, this was measured by an ion exchange method and determined to be 9.4 ± 0.1 [40].

This study also measured the pK1h of La(III) as 9.0 + 0.1 under similar conditions. Other studies show the first hydrolysis constant of La3+ to be 8.63 by different methods [41]. These studies suggest that the first hydrolysis constants are consistent with the charge densities of Ac3+ and La3+, indicating that Ac3+ is a "hard" metal ion. This information suggests the use of basic conditions for radiolabelling of Ac complexes.

Spectroscopically, Ac3+ is invisible to many forms of routine spectroscopy, such as ultraviolet-visible, fluorescence, electron paramagnetic resonance, etc., due to its electronic configuration (5f 0 6d 0). Ferrier et al., using the long-lived isotope Ac-227 (t1/2: 21.772 y), measured the L3-edge X-ray absorption near-edge structure (XANES), representing the first actinium XANES measurement. This study bodes well for the study of actinium via X-ray absorption spectroscopy (XAS) [42].

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The interpretation of the extended X-ray absorption fine-structure (EXAFS) data from room temperature solutions containing Ac in HCl demonstrated that the Ac3+ was coordinated to ~ 3 Cl− and ~ 6 H2O inner-sphere ligands. The calculated coordination numbers agreed with experimental values. This study showed that Ac tends to possess more Cl− inner sphere ligands than Americium, which is consistent with the notion that Ac3+ is substantially less polarising than the rest of the f-elements and confirms it as a hard acid. Later, the group reported an XAFS study wherein 10.9 + 0.5 water molecules were directly coordinated to the Ac3+ cation with an Ac-OH2O distance of 2.63 (1)Å [42]. This agreed with the Molecular Dynamics Density Functional Theory (MD-DFT) results.

Having 11 inner sphere water molecules is reasonable for the large Ac3+ ion; this is consistent with the coordination numbers determined by EXAFS for other +3 actinide and lanthanide aqua ions. The coordination number of 11 is also consistent with the current ligands and stable bismuth-209 [43].

Since Ac-225 itself cannot be detected directly with gamma spectroscopy, as it does not emit a detectable gamma ray, time must be allowed for the detectable daughter, Bi-213, to grow and be observed by gamma detection.

2.1.2.1. Chelating Agents for Actinium-225

The discovery of a chelating agent that binds Ac (III) with sufficient stability and controls the release of its daughter nuclides remains a challenge. Moreover, the limited global availability of Ac-225 and the absence of a stable surrogate nuclide have limited the study of this isotope to a handful of institutions worldwide that have secured a reliable Ac-225 supply. Most initial Ac-225 chelation studies have focused on screening a variety of commercially available polydentate macrocyclic or acyclic ligands for their ability to bind Ac-225 and form stable complexes in vitro or in vivo.

Despite the unique coordination preferences of the large +3 actinide, the literature reports very few studies investigating new ligands specifically designed to coordinate Ac(III).

Table 1 summarises ligands tested with Ac-225. (Table 1 Supplemental data).

2.1.2.2. Actinium-225 Labelled Nanoparticles

Researchers have sought to encapsulate the highly potent alpha-emitter into a nanoparticle structure to circumvent the inevitable loss of Ac-225 daughters after alpha decay from an actinium-chelate complex. It is hypothesized that the $^{225}Ac^{3+}$ ion and its decay daughters can be retained within the cavity of the nanoparticle structure. At the same time, the alpha particles are released and able to deposit their therapeutic dose at the intended target site.

However, using nanoparticles as a platform to affix radionuclides or other biomolecular targeting vectors comes with several limitations. The biodistribution of nanoparticles depends on their large size and ability to take advantage of the enhanced permeability and retention (EPR) effect of cancer cells, where 'leaky' vessels of poorly vascularized tumors allow for the uptake and retention of large macromolecules. Moreover, the relatively large particles are often primarily excreted through the hepatic pathway, which can cause unwanted high liver uptake. These challenges underscore the complexity of using nanoparticles in Ac-225 research and highlight the need for further investigation.

The accumulation of a highly toxic alpha-emitter in the liver may damage the organ. Much of the available literature describing Ac-225-labelled nanoparticles provides only in vitro data [44–48]. Below is a brief overview of some strategies for preparing Ac-225 radiolabelled nanoparticles.

The encapsulation of $^{225}Ac^{3+}$ ions in single-walled carbon nanotubes (SWNTs) by co-encapsulation of Gd3+ in an ion cluster was investigated. Although the Gd3+ ions remained inside the SWNTs, continual leakage of the $^{225}Ac^{3+}$ ions was seen when challenged with serum [45].

Some authors employed a multi-layered nanoparticle structure that can contain the recoiling daughters of the in vivo alpha generator at the centre cavity while coupling the outer layer to antibodies without preventing the release of emitted alpha particles. The shells included a radiation-resistant lanthanide phosphate crystal doped with Ac-225 and layered with a magnetic GdPO4 layer, plus a gold outer shell to attach targeting vectors [47].

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Polymer vesicles (polymersomes) composed of poly (butadiene-b-ethylene oxide) have also been used to encapsulate Ac-225 [47]. Preliminary in vitro studies in cells showed that smaller particles were absorbed by the cells and gathered around the cell nucleus. However, experiments and simulations indicated that larger polymerases are needed to retain recoiling daughters [47] correctly.

PEGylated liposomes loaded with Ac-225 and labelled with mouse anti-human PSMA J951 antibody or with the A10 PSMA aptamer were tested in vitro for their targeting, internalisation, and cytotoxicity on a prostate cancer cell line [48,49]. These studies demonstrated that anti-PSMA targeted liposomes loaded with Ac-225 can selectively bind, become internalised, and kill PSMA-expressing cells.

Similarly, Ac-225-loaded lipid-based nanocarrier was labelled with a PSMA-targeting antibody or small-molecule urea-based agent, and the targeting selectivity and cytotoxicity were compared to those of the radiolabelled antibody on its own [48]. It was found that the loaded lipid vesicles improved the killing efficacy threefold compared to the same levels of activity per cell when delivered by the PSMA-targeting antibody.

2.1.2.3. Assessing the Biodistribution of the Actinium-225 Decay Chain

When evaluating the performance of Ac-225 radiopharmaceuticals, the biodistribution of each alpha emission in the decay chain must be assessed. The retention or redistribution of francium-221 (Fr-221), astatine-217 (At-217), and Bi-213 at the target site impacts the radiopharmaceutical's efficacy and toxicity.

While the half-life of astatine-217 is short enough that its biodistribution can be assumed to be effectively identical to francium-221, the short half-life of francium-221 makes accurately determining its biodistribution—and also independently determining the biodistribution of its Bi-213 granddaughter—a challenge using conventional ex vivo counting methods.

Speedy harvesting and counting of organs are essential. While successive measurements of the same ex vivo tissue samples over time can be used to estimate the amount of francium-221 or Bi-213 present at the time of sacrifice, the uncertainty in these estimates increases the longer after sacrifice the first measurements are made [50].

Imaging-based methods can also help assess the biodistribution of the radionuclides in vivo, and quantitative SPECT imaging of Ac-225 progeny isotopes has been demonstrated on small-animal SPECT/CT systems for Bi-213 alone [51] and both francium-221 and Bi-213 simultaneously, via their 218 keV and 440 keV gamma lines, respectively [52]. Unfortunately, quantitative imaging of the high-energy Bi-213 photopeak (440 keV) requires a high-energy collimator unavailable on most imaging systems. However, qualitative SPECT imaging of Bi-213 has been performed clinically, as has qualitative francium-221 SPECT in preclinical settings [46,53–56].

Cerenkov imaging has also been demonstrated in vivo for the Ac-225 decay chain [57]. However, this imaging modality is incapable of quantitative biodistribution measurements and cannot distinguish between individual Ac-225 decay chain components.

While quantitative SPECT imaging of francium-221 and Bi-213 with the sub-millimeters spatial resolution has the potential to assess the retention of Ac-225 progeny within the tumor and determine uptake within whole organs [52], the short range of alpha particles means that information regarding the sub-organ biodistribution- a level of detail not provided by current in vivo imaging modalities - is necessary for alpha-particle dosimetry [58,59].

While ex vivo imaging using alpha-cameras can determine Ac-225 biodistributions with spatial resolutions sufficient for dosimetry [60–62], alpha particle dosimetry itself faces additional challenges that currently limit the translation of preclinical dosimetric data to biological outcomes in the clinic [58,59].

2.1.3. Preclinical Studies

List of relevant preclinical studies involving Ac-225 is shown in Table 2 Supplemental Data.

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2.1.4. Clinical Studies

For patients who have become resistant to β-irradiation treatments, α-particle targeted therapy (TAT) is a therapeutic option. α-particles have a high linear energy transfer (LET) (range 50 - 230 keV/μm), delivering solid ionisation along a linear track due to their double-positive charge. This explains the late years' great concentration of clinical studies in some neoplasia, like the final step of the whole chain of theragnostic new radiotracers research.

The consequence of high LET is increased toxicity on the target cell, implicitly with a higher probability of double-stranded DNA breakage, compared to β-particles with low LET.

DNA is the main target of high-LET α-particles, making α-particle cytotoxicity very practical. The particles cause rapid cell death with just a few crossings of the cell nucleus. The tissue range of the α particles is up to 100 μm, which allows the selective ablation of the targeted tumour cells, with minor consequences in terms of damage to the surrounding healthy tissues.

The emission of multiple alpha-particles in the Ac-225 decay chain (Figure 1) makes Ac-225 a particularly effective isotope to kill cancer cells, yet also challenges the directed delivery of the nuclide and its decay daughters. Due to the conservation of momentum, the emission of an energetic alpha particle (energies shown in Figure 1) imparts a recoil energy to the daughter nucleus, often >100 keV, 1000 times larger than the binding energy for any chemical bond [50]. The subsequent redistribution of the alpha-emitting daughter nuclides in vivo can cause substantial harm to untargeted healthy tissues and reduce the therapeutic effect. Renal toxicity caused by Bi-213 limits the use of Ac-225 in many clinical trials [63]. There are three main strategies for limiting the toxicity of recoil daughters in the literature: fast uptake and internalisation of the alpha emitters in the target tissue, encapsulation of the nuclide in a nanoparticle, or local administration of radioactivity directly into the target site via injection [50]. List of clinical studies involving Ac-225 reported in the database ClinicalTrials.gov is shown in Table 3 Supplemental Data.

2.1.5. Conclusion

The studies published until now demonstrate that, even though there was a greater concentration on prostate cancer and NET preclinical and clinical studies, some other tumoral types (like glioblastoma) still need preclinical and clinical development. The studies justify several pros and cons regarding the role of Ac-225 in TAT. Some observations, like the local administration, could be related to further insights into Ac-225 radiolabelled vector molecules studies in TAT.

2.2. Bismuth-213

2.2.1. Physical Characteristics

Bismuth belongs to Periodic Group 15 and has 35 isotopes. Most have short half-lives (from nanoseconds to a few minutes), and just one is deemed stable, bismuth-209, due to its extremely long half-life of 1.9·1019 years. From a clinical point of view, only bismuth-212 (Bi-212) and Bi-213 (Bi-213) have shown potential properties for research in targeted radionuclide treatment [1].

Bismuth-213 is one of the decay products of Ac-225 and has a physical half-time of 45.6 min. It decays into polonium-213 via β− emission (Eβ = 1.4 MeV, 97.84%) and into thallium-209 via α emission (Eα = 5.549 MeV, 0.16%, Eα = 5.869 MeV, 2.0%). polonium-213 and thallium-209 later undergo α and β decay respectively (Eα = 8.375 MeV, Eβ= 1.8 MeV) and transform into lead-209. The latter finally arrives at stable bismuth-209 through β- emission (Eβ= 0.6 MeV). The gamma emissions generated following the disintegration (440 keV, 26.1% emission probability) could be suitable for SPECT imaging and in vivo dosimetry [4].

The energy of the α particle emitted by the polonium-213, corresponding to an 85 μm path length in human soft tissue, is the major contributor to the total α emitted energy per disintegration and is primarily responsible for cytotoxic effects in Bi-213 TAT (targeted alfa therapy) [4,15].

Figure 3 reports a schematic representation of the decay chain of Th-229 to Ac-225 and Bi-213.

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To produce the short-lived Bi-213 (T1/2 = 45.6 min) on-site, Ac-225 can either be used directly as a therapeutic nuclide or set into Ac-225/Bi-213 generators [1]. The development of several types of these generators was based on selective separation of Bi-213 using cation and anion exchange or extraction chromatography [1].

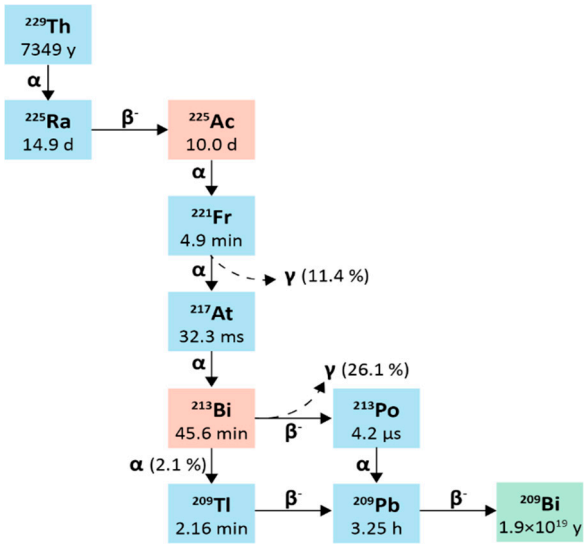

Figure 3. Schematic representation of the decay chain of Thorium-229 to Actinium-225, Ac-225, and Bi-213.

2.2.1.1. Actinium-225/Bismuth-213 Radionuclide Generators

To produce the short-lived Bi-213 (T1/2 = 45.6 min) on-site, Ac-225 can either be utilised directly as a therapeutic nuclide or set into Ac-225/Bi-213 generators [4,16]. All patient investigations with Bi-213 up to now have utilised Ac-225/Bi-213 generators. In this well-known approach, the parent Ac-225 in an acidic solution (for example, 0.05M HNO_3) is tightly bound by the sorbent (for example, AG MP-50 cation exchange resin), and Bi-213 is eluted [16]. To get Bi-213 in the forms of $^{213}BiI_4^-$ and $^{213}BiI_5^{2-}$ that may be employed immediately for radiochemistry uses, elution is often conducted with a mixture of 0.1M HCl/0.1M NaI. Furthermore, elution is permitted by the Ac-225/Bi-213's transitory equilibrium roughly every 3 hours [16,17].

The high-activity generator technology created at JRC Karlsruhe enables the generator to function reliably, even with up to 4 GBq of Ac-225 activities [4,16]. The yields of Bi-213 elution may be greater than 80%, while the parent nuclide (Ac-225) penetration through the generator (breakthrough) is less than 0.2 ppm (parts per million) in activity.

A way to minimise organic resin's radiolytic degradation and ensure its stable performance over several weeks is the process of the homogeneous distribution of Ac-225 activity over roughly two-thirds of the generator resin [5,17].

Injection-ready therapeutic dosages of Bi-213-labelled peptides with an activity of up to 2.3 GBq have been successfully prepared using the generator in clinical applications [16], for example, in the case of locoregional treatment of brain tumours [5]. Due to the relatively long parent half-life, which enables the generator to be transported to radiopharmacy facilities over vast distances, these generators may be employed clinically.

2.2.2. Radiochemistry

Bi-213 is a radiometal that requires a chelator with an extra reactive functional group to create a covalent connection with the vector molecule and, therefore, a stable complex [15].

Considering the short half-life of the radionuclide and the radioprotection requirements, it is also essential to use chelators suitable for fast and mild radiolabelling conditions to facilitate the

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manufacturing practice and the manipulation of Bi-213 radiopharmaceuticals. The possibility of using Bi-213 alone, chelator-free, is discouraged since it accumulates in the kidneys [64,65].

Due to the electronic configuration of [Xe] 4f14 5d10 6s2 6p3, the (+III) oxidation state is the most prevalent form of the bismuth ion, even though (+V) species have been described in some situations. As a hard Lewis acid, it strongly attracts hard donor atoms like oxygen or nitrogen, implying that chelating agents like amino polycarboxylate ligands would form stable complexes with Bi(III) [1].

Bismuth-213 can be stably linked to biomolecules via derivatives of DTPA (diethylene triamine pentaacetic acid) or DOTA (1,4,7,10-tetraazacyclododecane- 1,4,7,10-tetraacetic acid). The former shows rapid radiolabelling capability at room temperature. Still, it may have lower stability than DOTA, i.e. a higher risk of compound dissociation and unwanted biodistribution of unbound Bi-213 in the body.

Given that Bi-213 has a short half-life, reaction time is a critical parameter in radiolabelling chemistry. This was not an issue because of the quick complexation kinetics of DTPA (5 minutes at room temperature). However, in the case of DOTA complexation, high temperatures and a longer reaction time (30 minutes) are frequently necessary. Still, these conditions have been overcome by developing a radiolabelling procedure utilising microwaves that allows the complexation of Bi-213 in about 5 minutes at 95 C at pH = 9 [4]. The macrocyclic DOTA chelator is the gold standard bifunctional chelator, allowing for a compound stability of at least two hours [12]. Recently, cyclen-based chelators bearing phosphonic or phosphinic arms were described to form Bi-213-complexes in suitable reaction conditions (5 min, 25 ◦C or 95 ◦C, pH = 5.5), with high RCYs and promising stability at lower ligand concentration than DOTA or DTPA derivatives [1,66]. Chelators investigated in terms of Bi-213 complexation properties are reported in Figure 4 [66].

Alternatively, pyridine-containing azacrown ethers (Figure 5) showed similar results with fast complexation under mild conditions. Among these compounds, the results of in vitro serum stability and in vivo biodistribution studies suggest that the ligand L6 could be promising as a bifunctional chelator for radiopharmaceuticals labelled with Bi-213 [67].

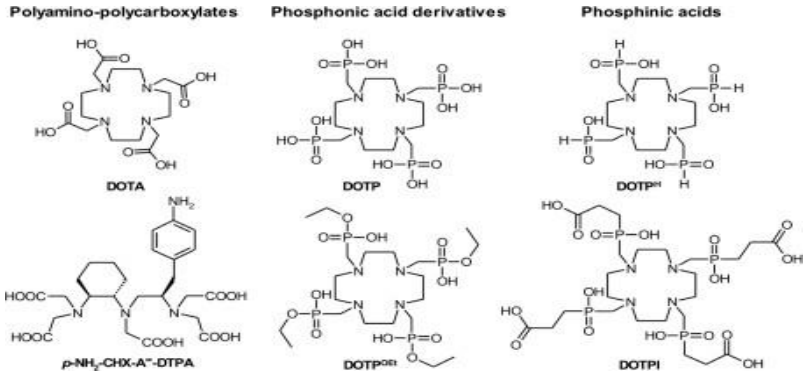

Figure 4. Chelators investigated for Bi-213.

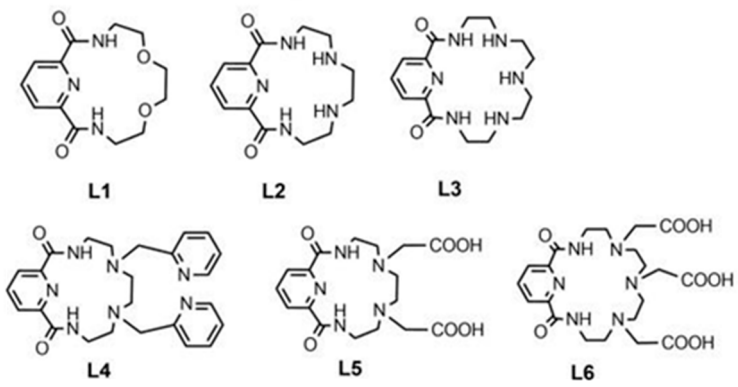

Figure 5. Pyridine-containing azacrown ethers for Bi-213.

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2.2.3. Preclinical Studies

Bismuth-213 was one of the first α-emitters to be studied, and the initial in vitro investigations at the beginning of the '90s have highlighted the potential of α-particles toward malignant cells [1]. A list of relevant preclinical studies involving Bi-213 is shown in Table 2 Supplemental Data.

2.2.4. Clinical Studies

Bismuth-213 was the first α-emitter to reach the clinical phase with the preparation of [^{213}Bi]Bi-lintuzumab for treating AML. In a Phase I trial, 18 patients with relapsed or refractory AML were treated with 10.36 to 37 MBq/kg of [^{213}Bi]Bi- lintuzumab. A rapid uptake was noticed in bone marrow, liver, and spleen, privileged sites of leukemic cells. Absorbed dose ratios between these areas and the whole body were measured to be 1000 times more important than analogue radioimmunoconjugates with β-emitters. Even if no complete remission was detected, a significant reduction of marrow blasts was noticed in 14 patients [54].

A phase I/II complementary study demonstrated that sequential administration of cytarabine before treatment with [^{213}Bi]Bi -lintuzumab injected doses (18.5 to 46.25 MBq/kg) could induce complete remission in some patients. These results are attributed to the cytarabine's ability to reduce tumour volume, improving the impact of radiation of [^{213}Bi]Bi – lintuzumab [68].

Thereafter, other applications and biological targets were investigated, but these data are not reported in the clinical trial database (ClinicalTrials.gov):

- Bi-213-radioimmunoconjugates (Bi-213-RICs) were also investigated for therapy of malignant melanoma [69].
- [^{213}Bi]Bi-cDTPA-9.2.27 showed an inhibitory effect on metastatic melanoma and no toxicity over the range of administered activities (55-947 MBq) [70,71].
- [^{213}Bi]Bi-HuM195 was also successfully attempted for acute myelogenous leukaemia or chronic myelomonocytic leukaemia (CML), involving: 93% of the treated patients had reductions in circulating blasts, and 78% experienced a decline in bone marrow blasts, with no significant extramedullary toxicity reported [54].
- [^{213}Bi]Bi-PSMA-617 for mCRPC, resulted in imaging response and a decrease in prostate-specific antigen levels, and [^{213}Bi]Bi-DOTATOC in neuroendocrine tumours refractory to beta emitter ^{177}Lu/^{90}Y-DOTATOC, which led to a significant reduction in targeting agent uptake, i.e. probable reduction of lesion size [55].

2.2.4.1. Locoregional Administration

A pilot study on the feasibility of Bi-213 radioimmunoconjugates (Bi-213-RICs) for the treatment of carcinoma in situ of the bladder refractory to bacillus Calmette-Guérin was conducted in 12 patients, showing no toxicity and a complete response for three patients, 44, 30 and 3 months after the administration [72]. Bismuth-213-DOTA-Substance P was locally injected in patients with recurrent glioblastoma multiforme. Treatment was safe and well tolerated, and median survival was superior to other alternative therapies [73]. A third example of locoregional injection of Bi-213-radiopharmaceutical was performed in the treatment of metastatic skin melanoma: significant reduction in serum marker melanoma-inhibitory-activity protein (MIA) at 2 weeks post-TAT was observed, and the therapy was safe and well tolerated [69].

2.2.5. Conclusion

Using Bi-213 bound to antibodies, peptides, and nanobodies showed optimal results in preclinical and clinical studies, with increased median survival and no relevant sign of toxicity. Bi-213 radiopharmaceuticals were tested and demonstrated efficacy in various malignancies, such as acute myelogenous leukaemia, mCRPC, and neuroendocrine tumours refractory to beta emitters.

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2.3. Astatine-211

Astatine is the rarest of all naturally occurring elements on Earth, situated below iodine in the periodic table. While only short-lived isotopes (t1/2 ≤ 8.1 h) are known, astatine-211 (At-211) is the object of growing attention due to its emission of high-energy alpha particles. Such radiation is highly efficient in eradicating disseminated tumours, provided that the radionuclide is attached to a cancer-targeting molecule. The interest in applications of At-211 in nuclear medicine translates into the increasing number of cyclotrons able to produce it. Yet, many challenges related to the minute amounts of available astatine must be overcome to characterise its physical and chemical properties. This point is of great importance for developing synthetic strategies and addressing the instability of the labelled compounds under the current approach, which limits the use of At-211-labelled radiopharmaceuticals. Despite its discovery in the 1940s, only the past decade has seen a significant rise in understanding astatine's basic chemical and radiochemical properties, thanks to the development of new analytical and computational tools.

2.3.1. Physical Characteristics

Astatine-211 decays with a 7.21 h half-life. It decays by 58.2% electron capture to short-lived Polonium-211 (T1/2 = 0.516(3) s) that decays in turn with 100% α emission to stable Lead-207. Moreover, At-211 decays by 41.8% α emission to quasi-stable Bismuth-207 (T1/2=31.6 years; only 26 Bq Bismuth-207 per 1 MBq of At-211 after decay of the latter) that decays in turn to stable Lead-207. Including its short-lived Polonium-211 daughter, the cumulative α emission is 100% per At-211 decay with an average α energy of 6.78 MeV.

The mean α energy per decay is 6785 keV, the mean recoil energy (of Bi-207 or Pb-207 recoils, respectively) is 131 keV, the mean electron energy per decay is 3 keV, and the mean photon energy per decay is 43 keV. Figure 6 reports a simplified At-211 decay scheme illustrating the double-branched pathway: by direct alpha decay to Bismuth-207 and by electron capture to Polonium-211, followed by alpha decay to Lead-207.

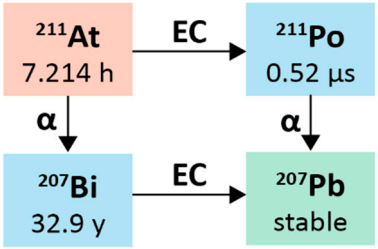

Figure 6. Simplified At-211 decay scheme.

An essential characteristic of At-211 that is different from most other α-emitters of relevance to Targeted Alpha Therapy (TAT) is that it yields one α-particle per decay, which offers certain translational advantages, including simplification of radiation dosimetry calculations for At-211-labelled TAT agents. Fortuitously, 58.2% of At-211 decays occur via electron capture to polonium-211, producing 77–92 keV polonium x-rays that permit counting At-211 activity with conventional gamma detectors and quantification of At-211 distribution in vivo by planar and SPECT imaging [62]. These x-rays allow measurement of At-211 biokinetics in patients, which can be used for safety and stability monitoring and organ-level assessment of radiation dosimetry of actual treatment doses. The Polonium-211 then decays with a 0.516-s half-life by emission of a 7.45 MeV α-particle to Pb-207, which is stable. The second At-211 decay branch (41.8%) involves the emission of 5.87 MeV α-particles to Bi-207 (T1/2 = 31.55-y), which likewise decays (by electron capture) to Pb-207.

Two aspects of the At-211 decay scheme could potentially be problematic – the Polonium-211 intermediate and the long-lived Bi-207 intermediate stated above. Concerning the first, one must consider the effects of an initial nuclear decay event on the fate of a subsequent α-particle emission.

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In the decay schemes where the first decay event is also by α-emission, the daughters would undergo chemical transformation, and the α-particle recoil energy would lead to escape and migration from the original decay site [50]. On the other hand, in At-211 decay, the Polonium-211 intermediate is the progeny of electron capture decay, which involves chemical transformation but insignificant daughter recoil energy. Even with the worst possible case assumptions – that this chemical transformation results in an instantaneous release of Polonium-211 from the cell surface and transport by unimpeded thermal diffusion- nearly 100% of Polonium-211 atoms should decay within two cell diameters from the original cell surface [74]. Since electron capture results in a highly charged daughter nucleus [75], which could impede diffusion, the diffusion distance from the original At-211 decay site might be even shorter. In any case, except in the rare instance where cancer presents for treatment as a single-cell distributed disease, the diffusion of the Polonium-211 daughter from the original decay site can be ignored. Second, the long half-life of the Bi-207 daughter could lead to potential issues due to its uptake in the bone, liver, and kidneys. However, this should also not be of concern because nearly 100,000 decays of At-211 are needed to produce a single decay of Bi-207 [76]. Thus, a 370 MBq (10 mCi) hypothetical patient dose of At-211-labelled TAT agent would generate ~4 kBq (~0.1 μCi) of Bi-207, a level that is only 0.1% of the 100 μCi Annual Limit of Intake (ALI) recommended for Bi-207 by the Nuclear Regulatory Commission, making its potential toxicity negligible.

The α-particle emission of At-211, with a mean linear energy transfer of about 100 keV μm−1, is like other TAT-candidate radionuclides [77]. This results in high relative biological effectiveness (RBE) because they can create more than 10 ionizations in a 100 Å diameter x 3 nm column [58,78], an ionization density close to the diameter of the DNA double helix. Even though At-211 emits fewer α-particles per decay than some other radionuclides under investigation for TAT, At-211-labelled targeted radiotherapeutics are exquisitely cytotoxic, with effective killing achievable with less than 10 atoms bound per cell [158]. Moreover, if uptake of At-211 in the cell nucleus can be achieved, the fact that At-211 also generates an average of 6.2 Auger electrons per decay (comparable to Ga-67) might be of therapeutic benefit [79].

2.3.2. Radiochemistry

One of At-211's most attractive properties, contributing to the emerging demand for this radionuclide, is the spectrum of targeting agents compatible with its labelling chemistry and physical half-life [80]. In contrast to other α-emitters, astatine is a halogen with similar chemical properties to iodine, albeit with more metalloid properties [81]. Astatine can exist in several oxidation states [82], providing multiple synthetic options but contributing to its sometimes confounding, capricious behaviour [83].

Although significant differences exist between astatine and iodine in labelling chemistry, carbon-halogen bond strength, lipophilicity, and the in vivo stability of carbon-halogen bond, they make it the most common strategy to develop At-211-labelled TAT agents to build on previous studies with radioiodine. Suppose one can demonstrate similar in vivo behaviour for the two labelled compounds. In that case, this suggests the possibility of using a radioiodinated analogue (I-124 for PET, I-123 for SPECT) as an imaging theragnostic partner for the corresponding At-211-labelled therapeutic. At-211 can readily be incorporated by direct substitution into small organic molecules, a potential advantage compared with radiometals, which require somewhat bulky polydentate ligands for stable incorporation. Two of the widely investigated approaches for At-211-labelling are the electrophilic demetallation of tin and silicon precursors [84] and carboranyl precursors [165]. Recently, a novel approach for At-211-labelling that involves Cu-catalysed astatination of boronic esters was demonstrated to have broad applicability, including the labelling of a PARP inhibitor [85]. Another method used a sulfonyl precursor for labelling neopentyl derivatives, providing high in vivo stability against nucleophilic substitution or Cytochrome P450 (CYP) metabolism [86].

As is the case with radiometals, biomolecules, including monoclonal antibodies, affibodies, diabodies, and nanobodies, can be labelled with At-211 using a variety of procedures [87]. For

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example, this can be accomplished via either the prototypical acylation agent N-succinimidyl 3-[^{211}At] astatobenzoate [88], using thiol-Michael addition for site-specific conjugation [89], or N-succinimidyl 3-[^{211}At] astato-5- guanidino methyl benzoate. This prosthetic agent provides intracellular radioactivity trapping after internalising receptor-targeted vectors [90,91].

Finally, the remarkable affinity of At-211 for gold has permitted the direct and nearly quantitative At-211-labelling of gold nanoparticles, which can be used alone or with targeting vectors decorating their surface [92]. In this account, we give a concise summary of recent advances in the determination of the physicochemical properties of astatine, putting in perspective the duality of this element, which exhibits the characteristics of both a halogen and a metal. Striking features were evidenced in the recent determination of its Pourbaix diagram, such as identifying stable cationic species, At+ and AtO+, contrasting with other halogens. Like metals, these species were shown to form complexes with anionic ligands and to exhibit a particular affinity for organic species bearing soft donor atoms. On the other hand, astatine shares many characteristics with other halogen elements. For instance, the At– species exists in water but with the least EH–pH stability range in the halogen series. Astatine can form molecular interactions through halogen bonding, and it was only recently identified as the strongest halogen-bond donor. This ability is nonetheless affected by relativistic effects, which translate to other peculiarities for this heavy element. For instance, the spin-orbit coupling boosts astatine's propensity to form charge-shift bonds, catching up with the behaviour of the lightest halogens (fluorine, chlorine).

All these new data impact the development of radiolabelling strategies to turn At-211 into radiopharmaceuticals. Inspired by the chemistry of iodine, the chemical approaches have sparsely evolved over the past decades and have long been limited to electrophilic halo-demetalation reactions to form astatoaryl compounds. Conversely, recent developments have favoured using the more stable At– species, including the aromatic nucleophilic substitution with diaryliodonium salts or the copper-catalysed halodeboronation of arylboron precursors.

However, new bonding modalities are necessary to improve the in vivo stability of At-211-labelled aryl compounds. The tools and data gathered over the past decade will contribute to instigating original strategies for overcoming the challenges offered by this enigmatic element. Alternatives to the C–At bond, such as the B–At and the metal–At bonds, are typical examples of exciting new research axes [93].

2.3.3. Preclinical Studies

List of relevant preclinical studies of At-211-labelled compounds is shown in Table 2 Supplemental Data.

2.3.4. Clinical Studies

The promising physical characteristics of the radionuclide led to early translation into clinical studies. The early studies were typically performed in a compassionate setting with exhausted available therapeutic options. Additional information about many of the most promising At-211-labelled radiopharmaceuticals that have been investigated for TAT applications, including those that have been evaluated in patients, can be found in several reviews.

As early as 1954 (less than 15 years after the discovery of At-211), the biodistribution of the radionuclide was investigated in a small series of 7 patients with thyroid disorders and a single patient with a locally advanced papillary adenocarcinoma of the thyroid [94]; while there was evident accumulation of the radionuclide in the thyroid gland after surgery, no accumulation was found in the regional lymph node metastases. After a substantial time gap, the radionuclide was used in 1990 to treat an unresectable relapsed carcinoma of the tongue using an intraarterial injection of At-211 labelled HSA microspheres, causing local necrosis of the tumour, later spreading to the rest of the tongue [95]. A series of patients (altogether 18) was treated in 1990 for the recurrence of glioma by injecting [^{211}At]At-labelled anti-tenascin molecule directly into the tumour cavity; time to progression was superior to the reports from the literature, including no physiological side effects [96]. Twelve

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patients with peritoneal metastases of ovarian carcinoma were treated in 2009 with [^{211}At]At -At-labelled antibodies against NaPi2b [62].

At-211-labelled antibody OKT10-B10 targets CD45 on several haematological malignancies and is being tested in patients with multiple myeloma, myelodysplastic syndrome, and several types of acute leukaemia, as well as a conditioning method before hematopoietic stem cell transplantation in non-malignant conditions to reduce graft rejection [97,98]. Meta-[^{211}At]At-benzyl guanidine (MABG) is expected to surpass the effectiveness of the [^{131}I]I-labelled alternative in systemic targeted therapy of metastatic pheochromocytoma/paraganglioma; up to 18 patients are planned [98]. Finally, At-211 is being investigated as an alternative to 131I in patients with differentiated thyroid cancer [99].

List of clinical studies involving At-211 reported in the database ClinicalTrials.gov is shown in Table 3 Supplemental Data.

2.3.5. Conclusion

An important characteristic of At-211 that is different from most other α-emitters relevant to Targeted Alpha Therapy (TAT) is that it yields one α-particle per decay, which offers certain translational advantages, including simplification of radiation dosimetry calculations for At-211-labelled TAT agents.

2.4. Lead-212

2.4.1. Physical Characteristics

Lead-212 has a half-life of 10.64 hours and decays through β- β-emission to bismuth-212, which in turn has a half-life of 60.5 minutes and decays through two pathways, each with one β- and one α-decay, as shown in Figure 7.

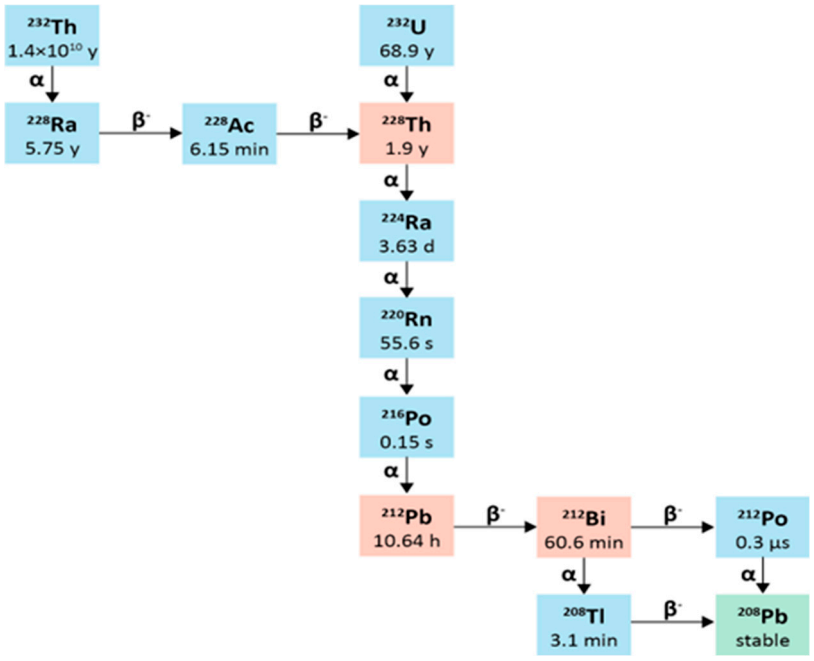

Figure 7. Decay scheme of thorium-232 and uranium-232.

The bismuth-212 β- decay (64% probability) produces polonium-212 with a half-life of just 0.3 µs, which decays by α emission to stable Pb-208. The other bismuth-212 decay route (36% probability) is through α emission to thallium-208 with a half-life of 3.05 mins, which decays to lead-208 via a β-β-emission.

There are also significant gamma emissions for the Pb-212 decay scheme that have implications for detection, handling, and safety. Lead-212 has emissions at 238.6 keV and 300.1 keV that enable

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Pb-212 to be detected during laboratory radiochemistry experiments and also are of suitable range for clinical gamma scintigraphy or SPECT/CT scanning, making quantitative measurements with Pb-212 possible [100] and enabling dosimetry. The decay product thallium-208 emits a very high-energy gamma (2614 keV) with 99.75 photons produced per 100 disintegrations. The short half-life of thallium-208 of just 3.05 mins also contributes to a high abundance of these high-energy emissions, which requires 15.5 mm of lead shielding to attenuate the radiation by half [101]. Therefore, it is essential to have adequate measures to ensure that operators minimise their exposure by reducing the time of operations, increasing their distance from the source, and using sufficient shielding. As thallium-208 is a decay product of Pb-212, the amount present in a source of pure Pb-212 will increase over time until equilibrium is reached with its progeny, which takes approximately 4 hours [102]. This also has implications for measuring the activity of purified Pb-212 present using an isotope calibrator, as the activity displayed will increase over time, and a calculated factor must be applied to the reading to accurately determine the activity of Pb-212 present in a sample [103]. When developing novel molecular radiotherapy agents, appropriate screening methods and accurate dosimetry are vital, so the existence of suitable radioisotopes that can be used for imaging is an advantage. Lead-203 offers this for Pb-212. Lead-203 has gamma emissions at 279 keV and a half-life of 51.9 hours, making it suitable for gamma cameras and SPECT imaging [104]. It can also be produced on a cyclotron from a solid thallium target using the $^{205}Tl(p,3n)^{203}Pb$ nuclear reaction with > 20 MeV protons [105].

2.4.2. Radiochemistry

Lead is a group 14 metal with a preferred oxidation state of 2+ and is amenable to chelation [106]. Although Pb-212 is used for targeted alpha therapy, it does not decay by alpha emission itself but by beta emission to yield the alpha emitter bismuth-212, as discussed above. To ensure both Pb-212 and Bi-212 are targeted and accumulate in disease sites, it is ideal for chelators of Pb-212 to remain bound to metals upon decay. Pb-212 has an advantage over alpha-emitting radionuclides in this respect, as the recoil energy of beta emission is in the range of 1 eV [107] compared to the 100,000 times higher recoil energy of an alpha emission (for example, the 212Bi alpha recoil energy is 108–117 keV [108]). While the recoil energy of an alpha emitter will undoubtedly break any bond between a chelator and a metal centre, the 1 eV recoil energy of beta particle emission is insufficient. However, dissociation of the 212Bi from the chelator can occur due to the sudden change in nuclear charge resulting from $[^{212}Pb]Pb^{2+}$ converting into $[^{212}Bi]Bi^{3+}$ or $[^{212}Bi]Bi^{5+}$ and the consequential valence electron shell reorganisation [107]. Experimentally, this has been observed for the DOTA chelator: when $[^{212}Pb]$Pb-DOTA decays to $[^{212}Bi]$Bi-DOTA, 36% becomes unchelated [110]. As Bismuth-212 has a 60.5-minute half-life, in-vivo redistribution of a proportion of free Bi-212 could occur if no additional cell trapping mechanisms, such as internalisation and residualisation, are at play. However, this is minor compared to the redistribution seen after alpha emission, and appropriate chelator design can potentially mitigate such issues for Pb-212.

Chelators suitable for Lead-203/Pb-212 include DOTA, TCMC (DOTAM) [106] and PSC [109] (Figure 8). These complexes will have a different charge when bound to lead (II), which is expected to alter the biodistribution of their corresponding bioconjugates. If one of the carboxyl groups were used for conjugation, the following complexes would result ([Pb(II)-DOTA-bioconjugate]1- [Pb(II)-TCMC-bioconjugate]1+, [Pb(II)-PSC- bioconjugate]0).

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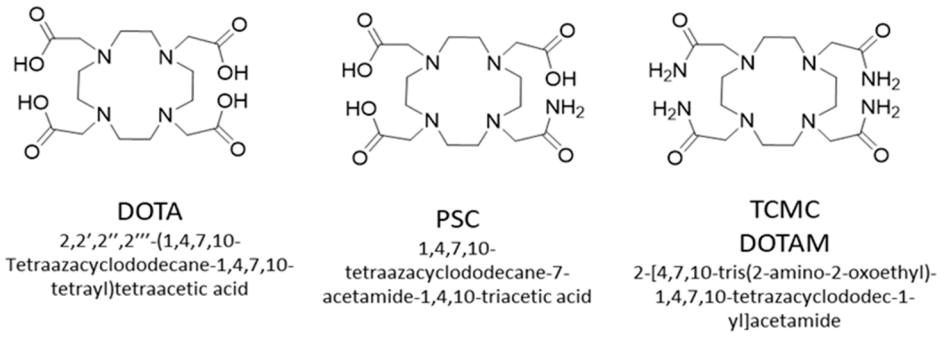

Figure 8. Chemical structures of DOTA, PSC and TCMC chelators.

Unlike other radionuclides, which are predominantly produced via irradiation using either a research reactor or an accelerator, Pb-212 is instead isolated from its parent radionuclides to create either a Ra-224/Pb-212 generator or a Th-228/Pb-212 generator. Both Ra-224 and Pb-212 are part of the Uranium-232 and Thorium-232 decay chain, in which some stockpiles have been created from naturally occurring uranium or previous civil or defence nuclear activities [104]. Several generators are under development with varying designs [110], but currently, the most widely available for research use is the Ra-224/Pb-212 generator from the United States Department of Energy Isotope program. This ion exchange generator contains AG MP-50 resin, loaded with up to 600 MBq of Ra-224 with a radionuclidic purity of >99.9%. The generator is eluted in hydrochloric acid. However, chloride salts of lead are poorly soluble, making radiolabelling difficult, so the first radiochemistry step is often the conversion to lead nitrate or lead acetate, which is achieved via evaporation and extraction, or solid phase extraction, respectively [110].

2.4.3. Preclinical Studies

List of relevant preclinical studies of Pb-212 -labelled compounds is shown in Table 2 Supplemental Data.

2.4.4. Clinical Studies

The first phase 1 clinical trial using Pb-212 was a trastuzumab bioconjugate labelled with Pb-212 via a TCMC chelator (NCT01384253) [111]. This was a safety and dose-escalation study where 18 patients with relapsed human epidermal growth factor receptor-2 (HER2) expressing peritoneal metastases were treated with a single intraperitoneal infusion of [^{212}Pb]Pb-TCMC-Trastuzumab and the agent was shown to be safe at all administered activities (7.4 - 27.4 MBq/m2, total activity 15-40 MBq) [111].

The first trial evaluating systemic, intravenously administered Pb-212 radiolabelled peptides was conducted using the Alphamedix bioconjugate [^{212}Pb]Pb-TCMC-TATE from RadioMedix and OranoMed, which targets somatostatin receptor-positive neuroendocrine cancers. The results of the phase 1 trial [112] of [^{212}Pb]Pb-TCMC-TATE (NCT03466216) were reported in 2021, and a phase 2 study is now open (NCT05153772). In the phase 1 trial, the highest administered activity was 2.5 MBq/Kg (max activity per cycle 203.5 MBq) for up to 4 cycles 8 weeks apart (maximum total activity per subject 888 MBq). The dosing regime was determined from a previous clinical study using [^{203}Pb]Pb-TCMC-TATE (unpublished), but patients for this study were screened with [^{68}Ga]Ga-DOTA-TATE [112]. This treatment was well tolerated with no severe treatment-emergent adverse events related to the study drug, and objective radiological responses were seen for 8 of 10 subjects treated at the highest activity regime for four cycles. Information about the dose delivered by this radiopharmaceutical to disease sites or dose-limiting organs is not yet available; dosimetry data were collected for six subjects enrolled in this trial and will be reported separately [112].

OranoMed has also opened a phase 1 clinical trial (NCT05283330) assessing the safety and tolerability of [^{212}Pb]Pb-DOTAM-GRPR1 in adults with cancers that express the gastrin-releasing

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peptide receptor BBR (Cervical Cancer, Prostate Cancer, Metastatic Breast Cancer, Colon Cancer, Non-Small Cell Lung Cancer, Cutaneous Melanoma). In 2023, two new early-phase trials have started recruiting to evaluate Pb-212 radiopharmaceuticals in metastatic castration-resistant prostate cancer: A) NCT05720130, a phase 1/2 safety and efficacy study of [^{212}Pb]Pb-ADVC001, for which AdvanCell Isotopes Pty Limited is the sponsor. This is being conducted in Australia, and B) NCT05725070, a Phase 0/1 Study, in Norway of [^{212}Pb]Pb-NG001, for which ArtBio is the sponsor.

More recently, Pb-203 is being used to scope the potential for new Pb-212 radiopharmaceuticals:

- [^{212}Pb Pb-VMT-α-NET ([^{212}Pb]Pb-PSC-PEG2-TOC) for somatostatin expressing neuroendocrine tumor (NCT06479811, NCT06427798)
- [^{212}Pb]Pb-VMT01 ([^{212}Pb]Pb- DOTA-PEG2-α-MSH for melanoma tumors expressing the melanocortin sub-type 1 receptor (MC1R) (NCT05655312) [113] .

List of clinical studies involving Pb-212 reported in database ClinicalTrials.gov is shown in Table 3 Supplemental Data.

2.4.5. Conclusion

Lead-212 is of high interest for TAT as an in-situ generator of the alpha emitter Bi-212 due to its well-matched half-life for peptide-based targeting moieties and the opportunity to conduct dosimetry studies with Pb-203. However, its most significant advantage is likely to become its wide availability due to stockpiles of its parent radionuclides and the investment in programmes to develop Th-228 /PbPb-212 and Ra-224 /PbPb-212 generators. Currently, there is limited preclinical and clinical data with PbPb-212, but the results obtained so far are very promising.

2.5. Terbium-149

The concept of using terbium-149 (Tb-149) for potential α-therapy and terbium-152 (Tb-152) for imaging/dosimetry was proposed by Beyer and Allen et al. in the late 1990s [114,115] and was further pursued by addressing the potential of terbium radioisotopes towards theranostics. The quadruplet of terbium radionuclides, i.e. Tb-152 (T1/2 = 17.5 h; PET) and Tb-155 (T1/2 = 5.3 d; SPECT) for imaging, while Tb-149 (T1/2 = 4.1 h; α-emitter) and Tb-161 (T1/2 = 6.9 d; β--emitter) proposed as potentially effective for radionuclide therapy, are recommended as true theranostic radiometals [116].

Terbium-149 represents a powerful alternative to the currently employed α-emitters [117]. These physical properties make it particularly well suited for application with small-molecular-weight targeting agents, including peptides, which are quickly cleared from the body [118]. The absence of α-emitting daughters is regarded as an additional favourable feature of Tb-149 since the toxicity of α- α-emitters with multiple α-emitting daughters has been identified as an issue for clinical application [50]. In vivo application of Tb-149 may, thus, be feasible without the risk of unspecific emission of harmful α-particles in the body as a consequence of released daughter radionuclides. The decay scheme of Tb-149 is complex [119], and the potential radiotoxicity of the resulting radio lanthanides remains to be determined [119].

2.5.1. Physical Characteristics

Terbium-149 decays in a complex decay scheme [120] with a half-life of 4.12 h, by emitting predominantly low-energy alpha-particles (3.97 MeV, 17%), EC-process (76%) and β+-emission (7%). Alpha-particle tissue range is around 25 μm and LET of 140 keV/μm. The absence of alpha-emitting daughters is a favorable feature of Tb-149 for clinical applications [50]. However, the daughter products of Teb-149 are long-lived radionuclides, like Gd-149 (9.28 d), Eu-145 (5.93 d), Sm-145 (340 d), Eu-149 (93.1 d), etc. More research is required to elucidate any complexity arising due to the in vivo presence of these Tb-149 decay products.

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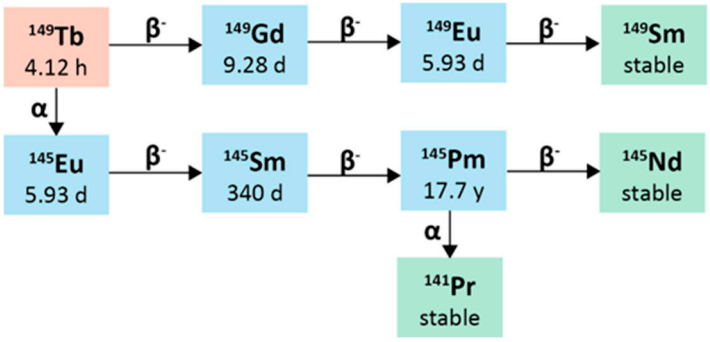

Figure 9. Simplified Tb-149 decay scheme.

2.5.2. Radiochemistry

As a trivalent radiolanthanide, Tb-149 can be stably coordinated with the conventional macrocyclic 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) chelator [116,121]. These circumstances allow the use of Tb-149 with DOTA-functionalized compounds that are (pre)clinically established for ^{177}Lu-based radionuclide therapy. Thus, existing approaches for labelling chelated bioconjugates with 177Lu, as well as with 166Ho, 153Sm, Bi-213 or Ac-225, can be directly applied to Tb-149.

Reactions to produce Tb-149 have been suggested using protons [122] and heavy ions [123–125], with reviews available [115,126,127].

Terbium-149 was produced in the spallation reaction Ta(p, spall) using the online isotope separator facility ISOLDE at CERN (Geneva, Switzerland) [128]. A tantalum-foil target (120 g/cm2) was irradiated with 1.0- or 1.4-GeV protons delivered from the CERN PS-Booster accelerator. The radio-lanthanides generated in the spallation process were released from the target material, which was kept at about 2,200°C, ionized by surface ionization and accelerated to 60 keV. From the obtained radioactive ion beams, the A=149 isobars (dysprosium-149, tTb-149 and molecular ions Ce(Ce-133)O+ and [^{133}La]LaO$^+$ were implanted (60 keV) and thus collected in thin layers of KNO3 (10 mg/cm2) on aluminium backings. The Terbium was separated from its daughters (Gadolinium-149 and Europium-145) and the pseudo-isobars Cesium-133 and Lantanum-133 by cation exchange chromatography using Aminex A5 resin and α-hydroxyisobutyric acid as eluent. The Tb-149 fraction (150–200 µl) was evaporated to dryness and re-dissolved in 50 µl of 100 mM HCl. The final Tb-149 concentration was 2 GBq/ml (54 mCi/ml) at the end of chromatographic separation (EOS).

Production of Tb-149 in the nuclear reactions ^{152}Gd(p,4n)^{149}Tb-149 and ^{142}Nd(12C,5n)^{149}Dy → Tb-149 at the U-200 cyclotron (LNR, JINR, Dubna) [115] was also experimentally confirmed. However, long-lived Eu, Pm, Gd, and Sm radionuclides in the Tb-149 decay chain and problems with Tb-149 production are significant drawbacks preventing the routine use of Tb-149 in nuclear medicine [129].

Recently, Tb-149 was produced by proton-induced spallation of a tantalum target, followed by an online isotope separation process at ISOLDE/CERN (Geneva, Switzerland). The mass-separated ion beam was implanted into a zinc-coated gold catcher foil, which was shipped to Paul Scherrer Institute (PSI, Villigen-PSI, Switzerland) for processing. As previously reported, Tb-149 was separated from isobar and pseudo-isobar impurities by cation exchange chromatography [116]. The separation yield was 100 MBq (~99 %) of highly pure Tb-149 in α-hydroxybutyric acid solution (pH 4.7), sufficient for preclinical application. The radiolabelling was carried out directly in the eluent solution by the addition of DOTANOC and incubation of the reaction mixture for 15 min at 95 °C. [^{149}Tb]Tb-DOTANOC was obtained with >98 % radiochemical purity at a high specific activity (5 MBq/nmol), as confirmed by high-performance liquid chromatography (HPLC)-based quality control [130].

As an alternative, it was proposed to obtain Tb-149 by irradiating Eu-151 targets with 3He nuclei and the thick target yields in the energy range 70 → 40 MeV were experimentally determined [131,132]. Preliminary results showed that Tb-149 yields can be high enough to produce therapeutic

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amounts of radionuclide. The method does not depend on mass separation and has the advantage of the availability of target material. Nevertheless, its drawback is the limited availability of high-intensity 3He beams, and it does not allow Tb-149 free of impurities, and its possibility of clinical application is yet to be proven [134,135].

2.5.3. Preclinical Studies

List of relevant preclinical studies involving Tb-149 is shown in Table 2 Supplemental Data.

2.5.4. Clinical Studies

Due to the valuable combination of physical characteristics (i.e., helpful alpha emission for therapeutic applications and positron emission for follow-up of distribution and possibly dosimetry), Tb-149 is one of the most promising radionuclides for clinical translation. The amount of injected activity is crucial for PET imaging. So far, the amount of activity required for therapeutic application in clinics is unknown. The sensitivity of the tumour type and other parameters will critically depend on the targeting agent and the degree of its accumulation in the tumour tissue. Whether the quantity of radioactivity would allow for PET imaging remains to be determined in patients [130]. The radionuclide's restricted availability has prevented the start of clinical trials, therefore to date there are no clinical studies documented in the database on ClinicalTrials.gov.

2.5.5. Conclusion

The unconventional production of Tb-149 was the main reason why Tb-149 had not yet reached clinical trials, as stated in several reports previously [3]. Currently, endeavours worldwide are focused on establishing new radionuclide production centres, clearly offering new perspectives for producing radionuclides like Tb, which are dependent on mass separation facilities. Such production centers, which exploit spallation production combined with isotope separation online (ISOL), are already in operation at the Isotope Separator and Accelerator (ISAC) at TRIUMF, Canada's National Laboratory for Particle and Nuclear Physics (Vancouver, Canada) and at Investigation of Radioactive Isotopes on Synchrocyclotron (IRIS), at the Petersburg Nuclear Physics Institute (PNPI, Gatchina, Russia). Other facilities are in the planning stage or under construction at the Radioactive Isotope Beam Factory (RIBF, East Lansing, U.S.), at the Belgium Nuclear Research Center ISOL facility (ISOL@MYRRHA, Mol, Belgium) and the Japan Proton Accelerator Research Complex (J-PARC ISOL, Tokai, Japan). MEDICIS, a new radionuclide production center dedicated to medical applications, is currently being built at CERN (Geneva, Switzerland) [20]. MEDICIS aims to produce medically interesting but not yet thoroughly investigated radionuclides, including Tb-149, in quantities sufficient to address the requirements of pilot investigations in patients. The perspective of overcoming the obstacle of production holds great promise for more detailed preclinical investigations and first clinical trials shortly using Tb for α- α-therapy, combined with PET.

2.6. Radium-223

2.6.1. Physical Characteristics

Radium-223 (half-life of 11.43 days) is formed naturally in trace amounts by the decay of uranium-235. It is usually produced artificially by exposing natural radium-226 to neutrons to produce Ra-227 (half-life of 42 min), which decays to Ac-227 (half-life of 21.8 years) and then via Th-227 (half-life of 18.7 days) to Ra-223. This decay path makes obtaining it from the Ac-227/Th-227 generator convenient. Radium-223 has a complex decay that produces 4 high-energy α particles, 2 β-particles and different Υ rays, with a total emitted energy of 28 MeV. The α particles contribute the most (95.3%) to this quantity and allow the deposition of a relevant absorbed dose. The decay scheme of Ra-223, including the closest radionuclide parents, is reported in Figure 10.

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The six-stage-decay of Ra-223 involving radon-219 (Ra-219) (half-life of 4 s), polonium-215 (half-life of 1.8 ms), lead-211(half-life of 36 min), bismuth-211 (half-life of 2.2 min) and thalium-207 (half-life of 4.8 min) leads to stable lead-207 and occurs via short-lived daughters, and is accompanied by several alpha, beta and gamma emissions with different energies and emission probabilities. The fraction of energy emitted from Ra-223 and its daughters as alpha-particles is 95.3% (energy range of 5.0 - 7.5 MeV). The fraction emitted as beta-particles is 3.6% (average energies are 0.445 MeV and 0.492 MeV), and the fraction emitted as gamma-radiation is 1.1% (energy range of 0.01 - 1.27 MeV).

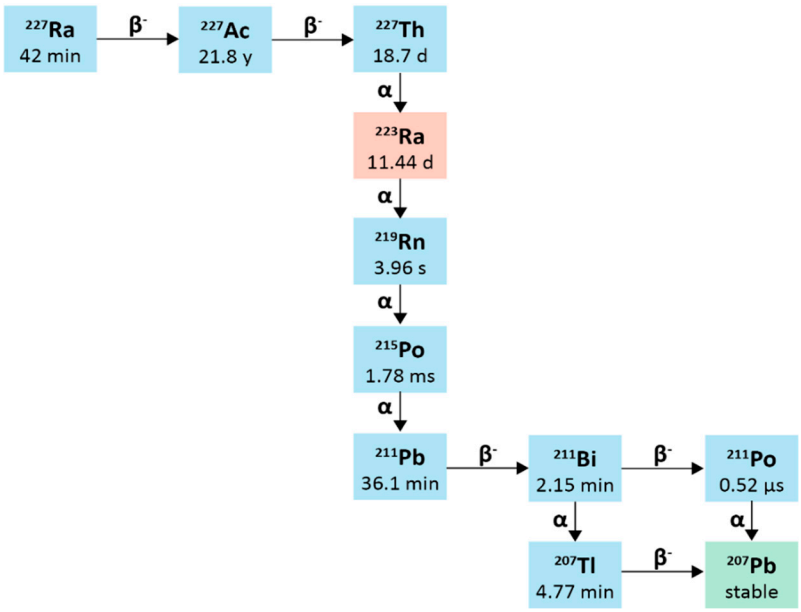

Figure 10. Radium-223 decay chain.

2.6.2. Radiochemistry

Radium is an alkaline earth metal with chemical properties similar to its homologues magnesium, barium, and calcium, and it exists mainly in the +2 oxidation state [2,133]. With a [Rn] 7s2 electronic configuration, the corresponding divalent cation Ra^{2+} is the only species formed. Concerning its potential chelation as a hard acceptor, a more pronounced affinity to complex donor atoms such as oxygen is expected [1]. Different compounds (DTPA, kryptofix 2.2.2, calix [4]-tetraacetic acid, DOTA) were tested as chelating agents for Ra^{2+} ion, but they all resulted in extremely unstable [134,137] and unsuitable for in vivo studies. However, Whilson and Thorec, in this work, showed that macropa, an 18-membered bis-picolinate diazacrown macrocycle, is an effective chelator of [Radium-223] Ra^{2+}demonstrating rapid complexation kinetics and profound in vivo stability. The authors also investigated Ra^{2+} chelation utilising a bifunctional derivative of macropa conjugated to a single amino acid, β-alanine, or a prostate cancer-targeting agent, DUPA [135]. The possibility of radiolabelling through encapsulation in biomaterials or nanomolecules [136] was also explored, using PEGylated liposomal doxorubicin, lanthanum phosphate nanoparticles (LaPO4) [283], iron oxide nanoparticles (Fe_2O_3) and nanozeolite NaA [133,137], barium sulfate ($BaSO_4$) [138,139], barium ferrite nanoparticles (BaFeNPs) [140], titanium dioxide (TiO_2) [141] and hydroxyapatite. Those solid-state nanoparticles stabilise [^{223}Ra]Ra^{2+} and alter their biodistribution properties. However, this scenario must be further investigated and tested in clinical studies. Ivanow and colleagues from Oak Ridge National Laboratory (ORNL) in Tennessee, US, used quantum chemical calculations that allow them to peer inside radium to see its electronic structure. They also examined how the ligand molecule orbitals overlap with vacant orbitals on radium. As a result, they found that the bonding is ionic and that electrostatic attraction plays a huge role [142]. Currently, Ra-223 is mainly used in its chloride salt form [^{223}Ra]$RaCl_2$, which naturally targets hydroxyapatite and bone matrix.

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2.6.3. Preclinical Studies

List of relevant preclinical studies involving Ra-223 is shown in Table 2 Supplemental Data.

2.6.4. Clinical Studies

Clinical studies in this context focused on the use [^{223}Ra]$RaCl_2$ for the treatment of mCRPC, especially in cases of chemotherapy or hormone therapy resistance. To date, the Phase III ALpharadin in SYMptomatic Prostate CAncer patients (ALSYMPCA) study is the trial with the largest cohort (n=921) of patients for the evaluation of Ra-223 antitumoral effect and survival analysis in cases of mCRPC. Patients in the Ra-223 arm, receiving six radiopharmaceutical injections at 55 kBq/kg every 4 weeks, showed longer overall survival and a longer time to a first skeletal event than those in the placebo arm [143,144]. Following the ALSYMPCA study, [^{223}Ra]$RaCl_2$ was validated by the FDA and EMA in 2013 for the treatment of bone metastases in mCRPC cases and became the first radiopharmaceutical approved for TAT. Evaluation of all secondary efficacy endpoints and myelosuppression also benefited the Ra-223-treated patients [144]. A large, randomised phase 3 trial (ERA 223) also assessed the combination of Ra-223 with abiraterone acetate plus prednisone or prednisolone: this combined therapy was associated with an increased frequency of bone fractures, so it was not recommended in mCRPC [145]. Based on the results of the ERA study, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) provided a benefit/risk review for Ra-223, which ended with a restriction of therapeutic indications (EPAR 11/10/2018) and confirmation of temporary contraindication measures. Due to the increased risk of fractures and possible increased mortality observed with the combination of Ra-223 with abiraterone acetate and prednisone/prednisolone, this triple combination remains contraindicated. Furthermore, the initiation of Ra-223 treatment is not recommended in the first 5 days following the last dose of abiraterone and prednisone/prednisolone. Subsequent systemic anticancer treatment should not be started for at least 30 days after the previous dose of Ra-223. Several combinations are currently studied in phase I or phase II trials, especially with enzalutamide (an androgen receptor signalling inhibitor) pembrolizumab (a monoclonal antibody againsPD1 protein) niraparib or olaparib (both are inhibitors of poly-ADP-ribose polymerase). Even if advanced prostate cancer is the primary pathology targeted with Radium-223, this radionuclide is under investigation in other pathologies associated with bone metastases, such as breast or renal cancer. The work on clinical applications with Ra-223 is considerable, and detailed reviews can provide more information about the global state of the art on Ra-223 and ongoing clinical trials [1]. Table 13 reports the main clinical studies involving Ra-223.

List of clinical studies involving Radium- 223 reported in database ClinicalTrials.gov is shown in Table 3 Supplemental Data.

2.6.5. Conclusion

The use of Ra-223 for treating bone metastases from mCRPC is largely diffused and standardised due to the FDA and EMA approval of [^{223}Ra]$RaCl_2$ in 2013. However, several combinations with monoclonal antibodies or different inhibitors are being studied, and the possibility of treating skeletal metastases from other primary tumours is being evaluated.

2.7. Thorium-227

2.6.1. Physical Characteristics

Thorium-227 is an alpha-emitting radionuclide with a physical half-life of 18.7 days. It is part of the actinium series, and it decays into Ra-223, releasing a 5.7 MeV (average energy) alpha particle. Four gamma emissions in the 200-350 keV energy range are associated with the decay, 236 keV (13%) being the most abundant. The latter can be used for imaging purposes, along with the 269 keV peak

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of the daughter radionuclide Ra-223 [133]. A summary of the decay of Th-227 is reported in Figure 11.

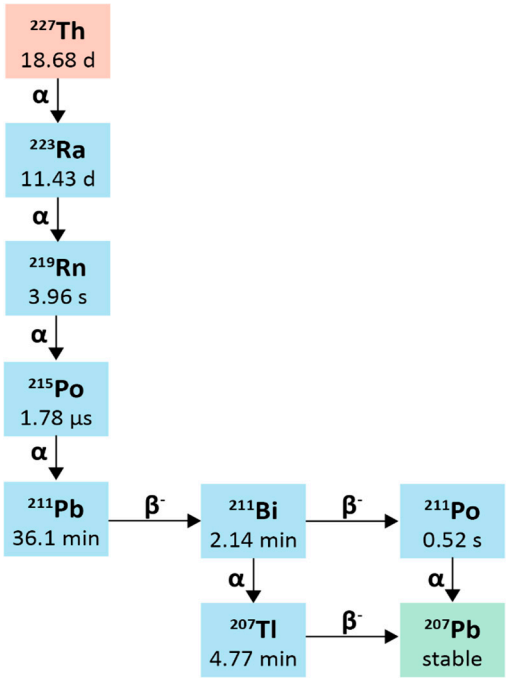

Figure 11. Decay scheme of Th-227.

2.7.2. Radiochemistry

Thorium-227 can have multiple oxidation states, but in the aqueous medium, the most stable one is +4. Free thorium showed high targeting capability for hydroxyapatite, a mineral form of calcium apatite largely present in vertebral bones. Still, its use has been discouraged considering its tendency to also accumulate in the kidneys [1]. Therefore, chelation with Phosphonate derivatives, which have a high affinity for bones, has been tested. More precisely, Th-227-complexes with DTMP, DOTMP and EDTMP demonstrated high and selective bone uptake and chemical stability [1,146]. The well-known DOTA also resulted in a suitable solution for Th-227 chelation, although high temperature and a two-step procedure were necessary. Different synthetic analogues were developed to overcome these limitations, the most promising one being hydroxypyridinone moiety (HOPO). In particular, polydentate HOPO ligands showed good stability and low in vivo toxicity [1].

2.7.3. Preclinical Studies

List of relevant preclinical studies involving Th-227 is shown in Table 2 Supplemental Data.

2.7.4. Clinical Studies

The literature of clinical trials involving Thorium-227-labelled agents is still limited, even though four phase I trials, registered in ClinicalTrials.gov are now completed:

- BAY2287411 (or MSLN-TTC) for solid tumors expressing mesothelin (NCT03507452),
- BAY2701439 (or HER2-TTC) for cancers with HER2 expression as breast cancer or gastric cancer (NCT04147819),
- BAY2315497 (or PSMA-TTC) for mCRPC (NCT03724747). Intermediate results from different studies have already been reported.

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- BAY 1862864, which is a [^{227}Th]Th-labelled CD22-targeting antibody, was injected into patients with CD22-positive relapsed/refractory B cell non-Hodgkin lymphoma (R/R-NHL) (NCT02581878), and the therapy resulted in safe and well-tolerated, with an objective response rate of 25% [150].

List of relevant clinical studies involving Th-227 is shown in Table 3 Supplemental Data.

2.7.5. Conclusion

The literature on clinical trials involving Th-227-labelled agents is still scarce, but optimal results were observed in preclinical studies with delays in cellular growth, multiple double-strand breaks, and complete regression. Intermediate phase I trial results are also reported, and safety, tolerability, and an objective response rate of 25% are shown.

3. Discussion and General Recommendations

1. Alpha-emitting radionuclides show great promise in reported clinical trials, leading to many clinical trials investigating these treatments. This demonstrates this is an area of great potential for patient benefit.

2. For clinical trials to progress using alpha-emitting radionuclides, access to a secure supply of these radionuclides must be sustained. The existing portfolio of trials has been driven as much by access to radionuclides of sufficient quality and quantity for GMP radiopharmaceutical production and scalability of the supply (which includes restrictions due to half-life) as by the properties of the radionuclide (such as chemical properties, decay scheme).

3. Many radionuclides considered in this review do not decay into a stable element but into radioactive progeny. The off-target effects are significant for dosimetry and radiation safety, and integration into the clinical trial design is essential.

4. Chelating agents or precursors for radiopharmaceuticals should be optimised for the alpha-emitting radionuclide used to ensure stability and minimise off-target effects due to the dissociation of "free" radionuclide. However, due to the large recoil energy created by alpha emission, if there is radioactive progeny, it will be released from the targeting moiety. This occurs both during transport to the hospital and after administration of the radiopharmaceutical, and the impact of this relationship should be considered during study design.

5. Dosimetry measurements should be an essential part of clinical trials using alpha-emitting radionuclides, and standardised methodology should be used.

6. To optimise the benefits of ongoing clinical trials, there should be standard ways to report trial results and standardised protocols within the trials.

7. Currently, the lack of clinical trial data in this area limits the recommendations about the most effective alpha-emitting radionuclides for a specific type/stage of disease. Given the promise that early studies have shown, further clinical trials should be supported in this area. These should also include sample collection to facilitate reverse translation and a deeper understanding of radiobiology.

4. Materials and Methods

The radionuclides considered for this report are Ac-225, Bi-213, At-211, Pb-212, Tb-149, Ra-223, and Th-227. This list was selected by SECURE consortium based on the potential clinical applications in the context of alpha-emitter-based therapies. Alpha emitters identified as clinical key players in the 2022 PRISMAP report, which surveyed European facilities and research institutions, were selected [148]. Moreover, a secondary search in literature and Symposium articles focused on the most promising alpha emitters in molecular radiation therapy confirmed this selection [1]. The decay schemes were reproduced from the same source: https://epa-prgs.ornl.gov/radionuclides/chain/chain.php. We conducted a literature search of the most important databases, including the selected radionuclides (some examples: European Medicines Agency (EMA) database, Medline, PubMed, Embase, Scopus, Clinical Trials.gov).

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Regarding criteria applied for literature search, to find the potentially relevant articles, the following keywords were used: "X-n" OR "alpha-emitter" OR "radionuclide therapy" OR "targeted alpha particle therapy" OR "radiolabelled therapy" OR "peptide receptor radionuclide therapy" AND "preclinical studies" AND "clinical studies" AND "physics characteristics" AND "radiochemistry. Only articles in the English language were included.

5. Conclusions

This document outlines comprehensive insights into the current landscape, methodologies, and applications of promising alpha-emitting radioisotopes in the clinical context. Seven alpha-emitting isotopes were studied: Ac-225, Bi-213, At-211, Pb-212, Tb-149, Ra-223, and Th-227. The detailed exploration of physical characteristics, radiochemical extraction, and clinical and preclinical studies across different isotopes demonstrates a multidisciplinary approach that combines nuclear physics, chemistry, and oncology to optimise cancer treatment. The therapeutic potential of alpha-emitting isotopes is recognised, particularly in targeting and destroying cancer cells, sparing surrounding healthy tissues, due to high LET and short range. This attribute is critical in the context of refractory cancers or metastatic diseases, where conventional therapies often fall short. However, the document also highlights significant challenges, including the complex radiochemistry involved in safely and effectively delivering these isotopes to target sites, the management of recoil daughter nuclides, and the critical issue of isotope availability. The latter is particularly pressing, given the intricate production and purification processes required for isotopes like Ac-225, which significantly impact scalability and accessibility.

The development of new chelating agents and the exploration of novel production methods, such as accelerator-based routes, are promising avenues that address current limitations in supply and isotopic purity.

Optimising production processes, improving isotopic stability, and ensuring safety will be crucial in transitioning from promising preclinical results to practical, scalable clinical applications.

The theranostic approach and the dosimetric evaluation also represent relevant challenges. Alpha-emitting radioisotopes often have complex decay chains and limited gamma emissions, resulting in difficulties in tracking all isotopes' daughters and their energy release and in configuring imaging settings. Gamma peaks may overlap, complicating the selection of an imaging peak in SPECT/CT systems and the quantification of activity and absorbed dose in regions of interest.

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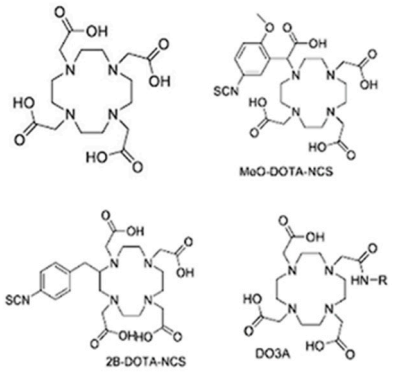
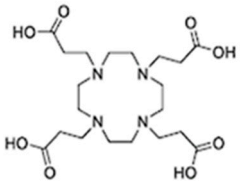
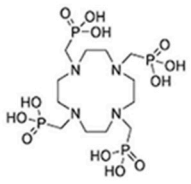
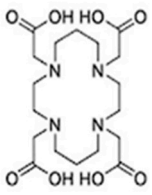
Appendix A. SUPPLEMENTAL DATA

Table 1. Tested Actinium-225 chelates coupled with targeting vectors for in vitro or in vivo application and their radiolabelling yields (RCY) and stabilities.

Chelate (and corresponding tested bifunctional analogues	Donor Set (CN#)	Grade	Radiolabelling Conditions & RCY	Ref.
DOTA 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid 	N_4O_4 **CN = 8**	Green - orange	0.02 M ligand, NH_4Ac pH 6, 37 °C, 2 h, RCY = 99%	[1]
DOTPA 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrapropionic acid 	N_4O_4 **CN = 8**	Red	0.02 M ligand, NH_4Ac pH 6, 37 °C, 2 h, RCY = 0%	[2]
DOTMP 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphinic acid 	N_4O_4 **CN = 8**	Red	0.02 M ligand, NH_4Ac pH 6, 37 °C, 2 h, RCY = 78%	[2]
TETPA 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrapropionic acid 	N_4O_4 **CN = 8**	Red	0.02 M ligand, NH_4Ac pH 6, 37 °C, 2 h, RCY = 0%	[2]

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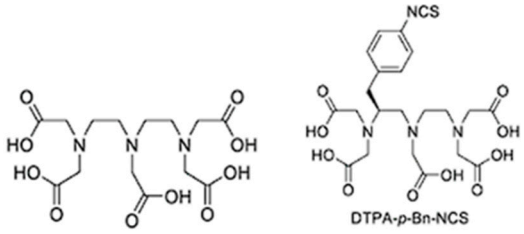
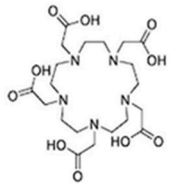
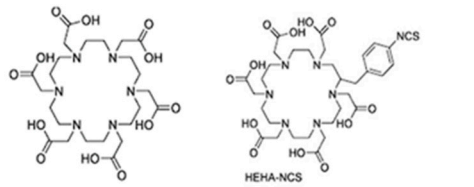
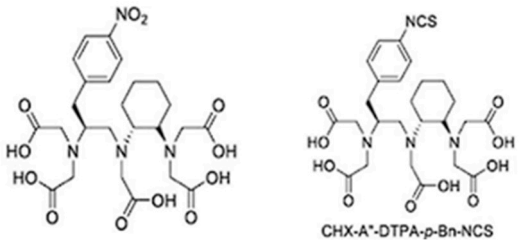
DTPA diethylenetriaminepentaacetic acid 	**N_3O_5** **CN = 8**	Red	0.02 M ligand, NH_4Ac pH 6, 37 °C, 2 h, RCY = 0%	[2]
EPA 1,4,7,10,13-pentaazacyclopentadecane-*N,N',N'',N''',N''''*-pentaacetic acid 	**N_5O_5** **CN = 10**	Red	0.02 M ligand, NH_4OAc pH 5.8, 40 °C, 30 min, RCY = 80%	[3]
HEHA 1,4,7,10,13,16-hexaazacyclohexadecane-N,N',N'',N''',N'''',N'''''-hexaacetic acid 	**N_6O_6** **CN = 12**	Orange	0.01 M ligand, NH_4OAc pH 5.8, 40 °C, 30 min, RCY > 95% or > 98% after 2 h	[3,4]
CHX-A''-DTPA 	**N_3O_5** **CN = 8**	Red	0.01 M ligand, NH_4OAc pH 5.8, 0.03 40 °C, 0.04 30 min, 0.05 RCY > 95%	[3,5]

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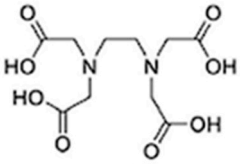
EDTA ethylenediaminetetraacetic acid  EDTA	N_2O_4 **CN = 6**	Red	1 M ligand, 2 NH_4OAc pH 5, 3 40 °C, 30 min, 4 RCY = 80-90%	[5]

Table 2. List of relevant preclinical studies.

	Preclinical model	Radiopharmaceutical	Activity/no of cycles	Main findings	Ref.
Ac-225	AR42J cells	[^{225}Ac]Ac -DOTA-CCK-66	37 kBq / 1 cycle	Substantial increase in mean survival of AR42J tumour-bearing mice upon treat-ment with the minigastrin derivative	[6]
Ac-225	Human ovarian carcinoma HER2-positive(SKOV-3 cell line)	[^{225}Ac]Ac -H$_4$py4pa	10.1±0.7 kBq / 1 cycle	Stability study, in vitro and biodistribution	[7]
Ac-225	Human breast cancer cell lines SUM-225 and MDA-MB-231	[^{225}Ac]Ac -DOTA-trastuzumab	0.37 kBq / 0.74 Bq / 1.48 Bq / 1 cycle	In vitro, biodistribution (comp. with In-111-DTPA-trastuzumab), optical imaging and therapy study.	[8]
Ac-225	Human HER2- positive cell lines SKOV-3 (ovarian cancer) and MDA-MB-231 (breast cancer)	[^{225}Ac]Ac- DOTA-Nb (nanobod)	30.2 ± 1.4 kBq / 1 cycle	In vitro and biodistribution In vitro, therapy study, dosimetry and toxicity	[9]
Ac-225	Human HER2- positive cell lines SKOV-3 (ovarian cancer) and MDA-MB-231 (breast cancer)	[^{225}Ac]Ac-DOTA-Nb (nanobod)	81.67 ± 28.87 kBq / 3 cycles	In vitro and biodistribution In vitro, therapy study, dosimetry and toxicity	[10]
Ac-225	U87mg human glioblastoma tumour cells	[^{225}Ac]Ac-DOTA-c(RGDyK)	10 kBq / 20 kBq / 40 kBq/ 1 cycle	Biodistribution, optical imaging and therapy study	[11]
Ac-225	Human glioblastoma cell line U251	[^{225}Ac]Ac-Pep-1L	40 kBq / 1 cycle	Bioluminescent imaging, therapy study (comparison with Cu-64-PepL1)	[12]

Ac-225	NT2.5 mammary tumour cell line	[^{225}Ac]Ac-DOTA-anti-PD-L1-BC	15 KBq / 1 cycle	Biodistribution (comparison with In-111-DTPA anti-PD-L1-BC), imaging, dosimetry	[13]
Ac-225	Human prostatic carcinoma cells LNCaP	[^{225}Ac,Ac-(macropa)]$^{+}$	26 kBq / 1 cycle	In vitro and biodistribution	[14]
Ac-225		[^{225}Ac,Ac-(macropa)]$^{+}$	37 KBq / 74 KBq / 148 KBq / 1 cycle	In vitro, biodistribution, therapy study and dosimetry	[15]
Ac-225	Human pancreatic cell line BxPC3	[^{225}Ac]Ac-DOTA Human antibody 5B1	18.5 kBq / 1 cycle	Biodistribution, luminescence imaging, therapy studies (pre-targeting or conventional) and toxicity	[16];[17]
Ac-225	Mammary carcinoma cell lines MFM-223 and BT-474	[^{225}Ac]Ac-hu11B6H435A	11.1 kBq / 1 cycle	In vitro, biodistribution and therapeutic study	[18]
Ac-225	Triple-negative breast cancer model SUM149T	[^{225}Ac]Ac-DOTA-cixutumumab	8.32 kBq / 1 cycle	In vitro, imaging, biodistribution (comp.with In-111-cixutumumab) and efficacy study	[19]
Ac-225	Malignant melanoma cell line B16F10	[^{225}Ac,Ac-octapa]$^{-}$[^{225}Ac,At-(CHXoctapa)]$^{-}$; [^{225}Ac,Ac(DOTA-CycMSH)]	12–20 kBq / 1 cycle	Stability study and biodistribution	[20]
Ac-225	Human cutaneous melanoma cells A375 andA375/MC1R and human uveal melanoma cells MEL270	[^{225}Ac]Ac-DOTA-MC1RL	148 kBq (±10%) / 1 cycle	In vitro, pharmacokinetic, biodistribution, therapy study and dosimetry	[21]
Ac-225	Human cutaneous melanoma cells A375 and A375/MC1R	[^{225}Ac]Ac-DOTA-Ahx-MC1RL (^{225}Ac-Ahx); [^{225}Ac]Ac-DOTA-di-d-Glu-MC1RL (^{225}Ac-di-d-Glu)	94.84 kBq ±7.11% / 56.52 kBq ±8.2 / 1 cycle	Biodistribution, pharmacokinetics, therapy study and toxicity	[22]
Ac-225	Malignant melanoma cell line B16F10	[^{225}Ac]Ac-DOTA-Anti-VLA-4	14.8 kBq / 1 cycle	In vitro, biodistribution, imaging dosimetry and therapeutic efficacy	[23]

Ac-225	Human embryonic kidney epithelial cells HEK-293T and HEK-293T-Hx16	[^{225}Ac]Ac-DOTA-(radioimmunoconjugate-Humanised site-specific antibodiesN149) SC16.56	18.9 – 55.5 kBq / 1 cycle	In vitro, biodistribution and efficacy study (comparison with Lu-177-DOTA-MMA)	[24]
Ac-225	Colorectal cancer (SW1222), breast cancer (BT-474) or neuroblastoma (IMR32)	[^{225}Ac]Ac-Proteus-DOTA (Humanised A33 and C825 (huA33-C825)	0, 9.25, 18.5, 37, 74, 148, or 296 kBq / 1 cycle	Biodistribution (comparison with ^{111}In-Pr, imaging) therapy study and toxicity(Pretargeted radioimmunotherapy)	[25]
Ac-225	Human pancreatic cell lines PANC-1 and MIA PaCa-2	[^{225}Ac]Ac-FAPI-04	34 kBq / 1 cycle	In vitro, biodistribution and efficacy study	[26]
Ac-225	Human squamous carcinoma A431 cell line	[^{225}Ac]Ac-DOTA-PP-F11N	45 kBq or 60 kBq / 1 cycle	In vitro, biodistribution and therapy study	[27]
Ac-225	Hepatoblastoma cell line HepG2 and squamous carcinoma A431 (GPC3+)	[^{225}Ac]Ac-Macropa-GC33	9.25 kBq or 18.5 kBq / 1 cycle	In vitro, biodistribution, therapy study and toxicity	[28]
Bi-213	Multiple myeloma	[^{213}Bi]Bi-anti CD138	3.7 MBq (single dose)	Increased median survival to 80 days, compared with 37 days for the untreated control group	[29];[30]
Bi-213	Bladder carcinoma	[^{213}Bi]Bi-anti-EGFR-mAb	0.94 MBq (fractioned dose)	Overall survival of 141.5 days on average, in contrast with 65.4 and 57.6 days for the two control groups	[31]
Bi-213	AR42J tumour- bearing mice; H69 human small-cell lung carcinoma; CA20948 rat pancreatic tumour	[^{213}Bi]Bi-DOTATATE	2–4 MBq/0.3 nmol/ 200 μL	Significant tumour burden reduction and improved overall survival	[32];[33]
At-211	syngeneic immunocompetent rat model	[^{211}At]At-BR96	2.5 or 5 MBq	Possibility of treating small, solid colon carcinoma tumours with tolerable toxicity	[34];[35]

At-211	U87MG cells Nude mice bearing xenograft tumours	[^{211}At]At-iRGD- C6-lys-C6-DA7R	180, 370 and 740 kBq	Inhibition of cell viability, induced cell apoptosis, arrested the cell cycle in the G2/M phase, and increased intracellular ROS levels in a dose-dependent manner; inhibition of tumour growth and prolongation of the survival of mice	[36]
At-211	T98G glioma cell line	[^{211}At]At-Rh [16aneS4]- SP5–11	75–1200 kBq/mL	Cytotoxic effect on glioma cells	[37];[32]
At-211	DBTRG-05MG glioma cell line, female BDIX rats with intracranial glioblastomas	2-[^{211}At]At-Phenylalanine 4- [^{211}At]At-Phenylalanine	1000 kBq (1 or 2 cycles)	Enhanced survival time of rats with intracranial glioblastomas	[38]; [39]
At-211	Athymic mice bearing subcutaneous D-54 MG human glioma xenografts	[^{211}At]At-ch81C6	74 kBq	Calculation of human radiation dose for i.v. and intrathecal administration	[40]
At-211	HNSCC-Bearing female nude mice (balb/c nu/nu)	[^{211}At]At-U36 (Chimeric mAb)	200 kBq	Specific binding to the glycoprotein and efficient therapeutic response	[41]
At-211	HL-60 and CI-1 cells	[^{211}At]At -rituximab; [^{211}At]At -gemtuzumab; [^{211}At]At gemtuzumab ozogamicin.	0.03 to 9.29 kBq (to 106 cells)	The affinity and specificity of the respective epitopes are not compromised	[42]
At-211	leukemic SJL/J mice	[^{211}At]At-30F11 (anti-murine CD45; mAb)	444, 740 and 888 kBq	Improvements in overall survival when combined with bone marrow transplantation in a disseminated	[43]

				model of murine leukaemia with minimal renal toxicity	
At-211	Female BALB/c mice	[^{211}At]At-30F11- ADTM	74, 370, 740 and 1850 kBq	more effective at myelosuppression than ^{213}Bi, no significant non hematopoietic toxicity	[44]
At-211	Human ML xenograft model in male hymic BALB/c nude mice	[^{211}At]At -CXCR4 (mAb)	320 kBq	clearance from blood and the tumour uptake matched the physical half-life of ^{211}At; tumour uptake was relatively low	[45]
At-211	Female and male NOD-Rag1null IL2rɣnull/J (NRG) mice	[^{211}At]At-B10 (conjugated anti-CD123; mAb)	185, 370, 740 or 1480 kBq	decreased tumour burden and significantly prolonged dose-dependent survival	[46]
At-211	Female athymic nude mice (s.c. injected Ramos cells)	[^{211}At]At-1F5- B10	Up to 1776 kBq	highly efficacious in minimal residual disease, no significant renal or hepatic toxicity	[47]
At-211	Normal Kunming (KM) mice, BALB/c nude mice (s.c. injected A549 cells)	[^{211}At]At -SPC-octreotide	2294 kBq	more lethal effect than control groups (PBS, octreotide and free ^{211}At), a possible treatment option for NSCLC	[48]
At-211	Human melanoma- xenografted nude mice	[^{211}At]At-MTB (methylene blue)	3,5 MBq	highly effective, no adverse effects of TAT	[49]
At-211	Female and male NOD.Cg Rag1tm1Mom Il2rgtm1Wjl/SzJ (NRG) mice	[^{211}At]At-OKT10- B10	277 to 1665 kBq	potential to eliminate residual MM cell clones in low-disease-burden settings with minimal toxicity	[50]

At-211	KaLwRij C57/BL6 mice (i.v. injected 5T33 cells)	[^{211}At]At-9E7.4	370, 555, 740 or 1110 kBq	the activity of 740 kBq showed 65% overall survival 150 days after the treatment with no evident sign of toxicity in MDR of multiple myeloma.	[51]
At-211	NB-EBC1x tumour- bearing mouse model (female SCID CB17 mice)	[^{211}At]At-parthanatine (PTT)	185 kBq	maximum tolerated dose (MTD 36 MBq/kg/fraction x4), complete tumour response was observed in 81.8% with reversible haematological and marrow toxicity	[52]
At-211	Male ICR mice (6 weeks old)	[^{211}At]At-MABG (astatobenzylguanidine)	185 kBq (biodistribution) 1.1, 2.2, 3.3, 4.4 MBq (body weigth studies)	the MTD was 3.3 MBq for ICR mice.	[53];[54]
At-211	female BALB/c nude mice s.c. inoculated with NIH: OVCAR-3 cells	[^{211}At]At-farletuzumab	700 kBq	the tumour-free fraction (TFF) was shown to be 91% for i.p. administered 211At-farletuzumab	[55]
At-211	nude Balb/c nu/nu mice (i.p. inoculated with OVCAR-3 cells)	[^{211}At]At-MX35 (mAb)	800 kBq and 3× ~267 kBq ~400 kBq and 3× ~133 kBq ~50 kBq or 3× ~17 kBq	no advantage in the therapeutic efficacy of a fractionated regimen compared with a single administration and lower side effects	[56]
At-211	nude Balb/c nu/nu mice (i.p. inoculated with OVCAR-3 cells)	[^{211}At]At-MX35 (mAb)	350 - 540 kBq	micrometastatic growth of an ovarian cancer cell line was reduced with no considerable signs of toxicity	[57]
At-211	nude Balb/c nu/nu mice (i.p. inoculated with SKOV-3 cells)	[^{211}At]At-trastuzumab (mAb)	100 – 800 kBq	statistically significant dose-response relationship for a single i.p. injection, a combination of 500 μg trastuzumab and 400 kBq ^{211}At-trastuzumab had the greatest effect	[58]

At-211	s.c. and PMGC (peritoneal metastasis of gastric cancer) xenograft mice	[^{211}At]At-trastuzumab (mAb)	100 and 1000 kBq	locoregionally administered [^{211}At]At-trastuzumab significantly prolonged the survival time	[59]
At-211	Female nude BALB/c (nu/nu) mice (s.c. inoculated with SKOV-3 cells)	N-succinimidyl- 3-[^{211}At]At-5-guanidinomethyl benzoate	700 kBq	fast and high accumulation in a HER2+ tumour mouse model with a low non-target organ uptake	[60]
At-211	female athymic mice (s.c. inoculation of 9BT474 xenografts)	Iso-[^{211}At]At SAGMB-5F7 Iso-[^{211}At]At SAGMB- VHH_2001	130 - 175 kBq	significant tumour growth delay and survival prolongation in a murine model of HER2-expressing breast cancer with no apparent normal- tissue toxicities	[61]
At-211	C.B17/Icr-scid mice (s.c. implantation of MDA-361/DYT2 cells)	[^{211}At]At-SAPS C6.5 (diabody); [^{211}At]At-SAPS T84.66 (diabody; [^{211}At]At-SAPS (anti-MISIIR GM17 diabody)	740, 1110 or 1665 kBq	single i.v. treatment resulted in dose-dependent delays in tumour growth	[62]
At-211	Athymicmice bearing PSMA+ PC3, PIP and PSMA- PC3 flu flank xenografts	(2S)-2-(3-(1-carboxy-5-(4-[^{211}At]At astatobenzamido)pentyl)ureido)-pentanedioic acid	200 kBq, 740 kBq	specific PC cell kill in vitro and in vivo after systemic administration and late nephrotoxicity	[63]
At-211	LNCaP xenograft mice, normal ICR mice	[^{211}At]At-PSMA1; [^{211}At]At-PSMA5;	110 – 400 kBq	[^{211}At]At-PSMA5 exhibited excellent tumour growth suppression in	[64]

		[^{211}At]At-PSMA6		xenograft models of prostate cancer, with minimal side effects.	
At-211	Male nude BALB/c nu/nu mice (s.c. inoculated with PC3- PSCA tumour cells)	[^{211}At]At-A11 (anti-PSCA mini body)	260 ± 20 kBq, 800 kBq and 1500 kBq	growth inhibition on both macro tumours and intratibial micro tumours and multiple fractions resulted in radiotoxicity	[65]
At-211	Male nude BALB/c nu/nu mice (s.c. inoculated with PC-3 cells)	[^{211}At]At-AB-3	85 kBq	poor in vivo stability	[66]
At-211	NIS-6 cells	[^{211}At]At-astatide	50-100 kBq	uptake is shown to be NIS-dependent	[67];[68]
At-211	NMRI-nu/nu nude mice (s.c. inoculated with xenografts of a human papillary thyroid carcinoma cell line, K1)	[^{211}At]At-astatide	100, 500 and 1000 kBq	high tumouricidal potential in NIS gene–transfected tumours without major side effects	[69]
At-211	Healthy male Balb/C nu/nu mice	[^{211}At]At-AuNP (gold nanoparticles)	900 kBq	high in vitro and in vivo stability	[70]
At-211	Male nude BALB/c- nu-nu (s.c. inoculated PANC-1 cells)	[^{211}At]At-FAPI-1; [^{211}At]At- FAPI-5	540 – 970 kBq	higher tumour retention of [^{211}At]At-FAPI(s) compared with [^{131}I]I -FAPI(s)	[71]
Pb-212	Model A - Female naïve CD-1Elite mice; Model B – Female Athymic mice bearing AR42J tumour Xenografts	[^{212}Pb]Pb-PSC-PEG-T	Model A- Single injection of 74 kBq; Model B- Single injection of 3.7 MBq	Model A - fast clearance from blood circulation, cleared through the kidneys. Model B - prolonged accumulation in tumour and minimal retention in kidneys (0.9%ID in tumour; 1%ID in kidneys)	[72]

Pb-212	Female athymic-NCR- nude mice with SK-OV-3 tumour xenografts: Model A - tumour volume 15 mm3 Model B – tumour volume 146 mm3	[^{212}Pb]Pb-DOTA-AE1	Model A - Single injection of 740 kBq; Model B – Single injection of 925 kBq	Model A – the rate of tumour growth was inhibited in the period after the [^{212}Pb]Pb-DOTA-AE1 therapy; Model B - [^{212}Pb]Pb-DOTA-AE1 did not provide effective therapy for large established tumours.	[73]
Pb-212	Male non-obese, diabetic/Shi-scid/IL- 2rgnull (NSG) mice: Model A - bearing PSMA(+) PC3 PIP tumour xenografts. Tumour volume 60–100 mm3. Model B - PSMA(+) micrometastatic model, mice were injected intravenously with 1 x 106 PC3-ML-Luc-PSMA cells	[^{212}Pb]Pb-L2	Model A - Single dose of 3.7 MBq Model B - 0, 0.7, 1.5, or 3.7 MBq	Model A - A single administration of 1.5 or 3.7 MBq showed significant tumour growth delay only in PSMA(+) Model B - the median survival time for the mice administered [^{212}Pb]Pb-L2 (3.7 MBq) was 58 days, demonstrating moderate but significant improvement.	[74]
Pb-212	Athymic Nude-Foxn1nu mice bearing C4-2 tumour xenografts. Tumour volume 250-1000 mm3	[^{212}Pb]Pb-NG001; [^{212}Pb]Pb-PSMA-617	Single dose of 10-56 kBq of [^{212}Pb]Pb-NG001; A single dose of 79 kBq of [^{212}Pb]Pb-PSMA-617	The uptake values (%ID/g) for tumour and kidneys at 2-hour post-injection were 17.61±6.76 and 21.07±10.33 for [^{212}Pb]Pb-NG001 and 17.93±2.90 and 52.82±26.62 for [^{212}Pb]Pb-PSMA-617	[75]
Pb-212	SCID mice bearing PC3 tumour xenografts	[^{212}Pb]Pb-RM2	Single dose of 1.85 MBq or 3.7 MBq	Both [^{212}Pb]Pb-RM2 treatment groups (1.85 MBq or 3.7MBq) demonstrated initial tumour control	[76]

				for 4-5 weeks post-treatment. 18 days pi, tumour regression was observed in the 3.7 MBq group (maximum per cent change of -49.3%) 40 days pi, tumour regrowth was observed in the 3.7 MBq group (+91.6% change from predose)	
Tb-149	SCID mouse model of leukaemia	[^{149}Tb]Tb-rituximab	5.5MBq labelled antibody conjugate (1.11GBq/mg) 2 days after an intravenous graft of 5106 Daudi cells	Tumour-free survival for >120 days in 89% of treated animals	[77]
Tb-149	Tumour-bearing mice	[^{149}Tb]Tb-cm09 (DOTA-folate conjugate)	Group A: saline only Group B: 2.2 MBq; Group C: 3.0 MBq;	A significant tumour growth delay was found in treated animals resulting in an increased average survival time of mice which received 149Tb-cm09 (B: 30.5 d; C: 43 d) compared to untreated controls (A: 21 d).	[78]
Ra-223	Balb/c	[^{223}Ra]$RaCl_2$	450 kBq/kg of ^{223}Ra	High activity concentration in bone; High retention in the kidney and spleen among OARs	[79]
Ra-223	Balb/c	[^{223}Ra]$RaCl_2$	1250, 2500, 3750 kBq/kg	Minimal to moderate depletion of osteocytes and osteoblasts	[80]
Ra-223	Intratibial LNCaP or LuCaP 58	[^{223}Ra]$RaCl_2$	300 kBq/kg	Inhibition of tumour cellular growth	[81]

			– 2 cycles		
Th-227	Human lymphoma Raji	[^{22t}Th]Th -Rituximab	50, 200, 1000 kBq/kg	Complete regression in 60% of mice treated with 200 kBq/kg	[82]
Th-227	HER2-overexpressing subcutaneous SKOV-3 or SKBR-3	[^{22t}Th]Th-trastuzumab	1000 kBq/kg - 1 cycle; 250 kBq/kg - 4 cycles	Survival with a tumour diameter of less than 16 mm was prolonged	[83]
Th-227	subcutaneous xenograft mouse model using HL- 60 cells at a single dose regimen	[^{22t}Th]Th-CD33-TTC	50, 150, or 300 kBq/kg – 1 cycle a second injection of 150 kBq/kg for some animals	Dose- dependent significant survival benefit	[84]
Th-227	NCI-H716, SNU- 16, and MFM-223	[^{22t}Th]Th-FGFR2-TTC	500 kBq/kg	significant inhibition of tumour growth at a dose of 500 kBq/kg	[85]

Table 3. Overview of some of the current/ongoing clinical studies registered in ClinicalTrials.gov.

NCT Number	Radio	Radiopharmaceutical	Study Title	Study Status	Conditions	Sponsor	Phases
NCT06939036	Ac-225	[^{225}Ac]Ac-SSO110	Study of [^{225}Ac]Ac-SSO110 in Subjects With ES-SCLC or MCC (SANTANA-225)	Ongoing, estimated completion 2026-12	Small Cell Lung Cancer Extensive Stage|Merkel Cell Carcinoma	Ariceum Therapeutics GmbH	Phase I/II
NCT06888323	Ac-225	[^{225}Ac]Ac-lintuzumab	Testing an Anti-cancer Radio-Active Immunotherapy Called [^{225}Ac]Ac-lintuzumab in Patients With High-Risk Myelodysplastic Syndrome That Has Not Responded to Other Treatment	Not yet recruting	Refractory Myelodysplastic Syndrome	National Cancer Institute (NCI)	Phase I

NCT06881823	Ac-225	[^{225}Ac]Ac-PSMA-R2 (AAA802); [^{177}Lu]Lu-PSMA-R2 (AAA602)	Study to Assess [^{177}Lu]Lu-PSMA-R2 (AAA602) and [225Ac]Ac-PSMA-R2 (AAA802) in Participants With PSMA-positive HRLPC	Not yet recruting	Prostate Cancer	Novartis Pharmaceuticals	Phase I/II
NCT06879041	Ac-225	[^{225}Ac]Ac-AZD2284	A Phase I Study of [^{225}Ac]Ac-AZD2284 in Patients With Metastatic Castration-Resistant Prostate Cancer	Ongoing, estimated completion 2029-04	Metastatic Castration-Resistant Prostate Cancer	AstraZeneca	Phase I
NCT06802523	Ac-225	[^{225}Ac]Ac-lintuzumab	Testing the Combination of Targeted Radiotherapy With Anti-Cancer Drugs, Venetoclax and ASTX-727, to Improve Outcomes for Adults With Newly Diagnosed Acute Myeloid Leukemia	Not yet recruting	Acute Myeloid Leukemia	National Cancer Institute (NCI)	Phase I
NCT06736418	Ac-225	[^{225}Ac]Ac-ABD147	Study of [^{225}Ac]Ac-ABD147to Establish Optimal Dose in Patients With SCLC and LCNEC of the Lung That Previously Received Platinum-based Chemotherapy	Ongoing, estimated completion 2027-01	Small-Cell Lung Cancer (SCLC)|Large Cell Neuroendocrine Carcinoma of the Lung	Abdera Therapeutics Inc.	Phase I
NCT06726161	Ac-225	[^{225}Ac]Ac-RYZ811; [^{225}Ac]Ac-RYZ801	Study of the Theranostic Pair RYZ811 (Diagnostic) and RYZ801 (Therapeutic) to Identify and Treat Subjects With GPC3+ Unresectable HCC	Ongoing, estimated completion 2031-01	HCC	RayzeBio, Inc.	Phase I

NCT06590857	Ac-225	[^{225}Ac]Ac-DOTATATE (RYZ101)	Trial of [^{225}Ac]Ac-DOTATATE (RYZ101) in Subjects with ER+, HER2-negative Unresectable or Metastatic Breast Cancer Expressing SSTRs.	Ongoing, estimated completion 2033-01	Metastatic Breast Cancer HER2-negative ER+	RayzeBio, Inc.	Phase I/II
NCT06287944	Ac-225	[^{225}Ac]Ac-DOTA-Daratumumab	[^{225}Ac]Ac-DOTA -Anti-CD38 Daratumumab Monoclonal Antibody With Fludarabine, Melphalan and Total Marrow and Lymphoid Irradiation as Conditioning Treatment for Donor Stem Cell Transplant in Patients With High-Risk Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia and Myelodysplastic Syndrome	Ongoing, estimated completion 2028-05	Acute Lymphoblastic Leukemia; Acute Myeloid Leukemia; Myelodysplastic Syndrome	City of Hope Medical Center	Phase I
NCT06229366	Ac-225	[^{225}Ac]Ac-PSMA-62	[^{225}Ac]Ac-PSMA-62 Trial in Oligometastatic Hormone Sensitive and Metastatic Castration Resistant Prostate Cancer	Ongoing, estimated completion 2027-09	Prostate Cancer	Eli Lilly and Company	Phase I
NCT05983198	Ac-225	[^{225}Ac]Ac-PSMA-R2	Phase I/II Study of [225Ac]Ac-PSMA-R2 in PSMA-positive Prostate Cancer, With/Without Prior [^{177}Lu]Lu-PSMA RLT (SatisfACtion)	Ongoing, estimated completion 2029-11	mCRPC treated with prior ARPI in post- 177Lu and pre-177Lu settings	Novartis Pharmaceuticals	Phase I/II

NCT05605522	Ac-225	[^{225}Ac]Ac-FPI-2059	A Study of [^{225}Ac]Ac-FPI-2059 in Adult Participants With Solid Tumours	Active not recruting, estimated completion 2025-09	NTSR1-positive solid tumours refractory to standard therapies	Fusion Pharmaceuticals Inc.	Phase I
NCT05595460	Ac-225	[^{225}Ac]Ac-DOTATATE (RYZ101)	Study of RYZ101 in Combination With SoC in Subjects With SSTR+ ES-SCLC	Ongoing, estimated completion 2029-03	SSTR2-positive extensive-stage small- cell lung cancer	RayzeBio, Inc.	Phase I
NCT05567770	Ac-225	[^{225}Ac]Ac-J591	Actinium-J591 Radionuclide Therapy in PSMA-Detected Metastatic HOrmone-Sensitive Recurrent Prostate CaNcer	WITHDRAWN	Prostate Cancer Metastatic	Weill Medical College of Cornell University	Phase I
NCT05477576	Ac-225	[^{225}Ac]Ac-DOTATATE (RYZ101)	Study of RYZ101 Compared With SOC in Pts w Inoperable SSTR+ Well-differentiated GEP-NET That Has Progressed Following 177Lu-SSA Therapy	Ongoing, estimated completion 2028-07	SSTR2-positive gastroenteropancreatic neuroendocrine tumours with prior 177Lu therapy	RayzeBio, Inc.	Phase III
NCT05363111	Ac-225	[^{225}Ac]Ac-DOTA-daratumuab	Radioimmunotherapy [^{111}I]I/[^{225}Ac]Ac-DOTA - daratumumab) for the Treatment of Relapsed/Refractory Multiple Myeloma	Ongoing, estimated completion 2025-06	Relapsed or refractory multiple myeloma after at least 2 lines of prior therapy	City of Hope Medical Center	Phase I
NCT05219500	Ac-225	[^{225}Ac]Ac-FPI-2265 (PSMA-I&T)	Targeted Alpha Therapy With [^{225}Ac]Ac-FPI-2265-Prostate Specific Membrane Antigen (PSMA)-I&T of Castration-	Active, not recruting, estimated completion 2025-07	mCRPC with prior ARPI	Fusion Pharmaceuticals	Phase II

			resISTant Prostate Cancer (TATCIST)				
NCT05204147	Ac-225	[^{225}Ac]Ac-DOTA-M5A	Actinium 225 Labeled Anti-CEA Antibody ([^{225}Ac]Ac-DOTA-M5A) for the Treatment of CEA Producing Advanced or Metastatic Cancers	Ongoing, estimated completion 2025-08	Metastatic solid tumours expressing CEA	City of Hope Medical Center	Phase I
NCT04946370	Ac-225	[^{225}Ac]Ac-J591	Phase I/II Trial of Pembrolizumab and Androgen-receptor Pathway Inhibitor With or Without [^{225}Ac]Ac-J591for Progressive Metastatic Castration Resistant Prostate Cancer	Ongoing, estimated completion 2028-06	mCRPC treated with prior ARPI	Weill Medical College of Cornell University	Phase I/II
NCT04886986	Ac-225	[^{225}Ac]Ac-J591 with [^{177}Lu]Lu-PSMA-I&T	Phase I/II [^{225}Ac]Ac-J591 Plus [^{177}Lu]Lu-PSMA-I&T for Progressive Metastatic Castration Resistant Prostate Cancer	Suspended, estimated completion 2027-12	mCRPC treated with prior ARPI	Weill Medical College of Cornell University	Phase I/II
NCT04644770	Ac-225	[^{225}Ac]Ac DOTA-h11B6 (JNJ-69086420)	A Study of JNJ-69086420, an Actinium-225-Labeled Antibody Targeting Human Kallikrein-2 (hK2) for Advanced Prostate Cancer	Ongoing, estimated completion 2025-12	mCRPC with prior ARPI	Janssen Research & Development, LLC	Phase I
NCT04597411	Ac-225	[^{225}Ac]Ac-PSMA-617	Study of [^{225}Ac]Ac-PSMA-617 in Men With PSMA-positive Prostate Cancer	Ongoing, estimated completion 2027-01	mCRPC	Endocyte	Phase I

NCT04576871	Ac-225	[^{225}Ac]Ac-J591	Re-treatment [^{225}Ac]Ac-J591for mCRPC	Active non recruting, estimated completion 2026-12	mCRPC treated with prior ARPI	Weill Medical College of Cornell University	Phase I
NCT04506567	Ac-225	[^{225}Ac]Ac-J591	Fractionated and Multiple Dose [^{225}Ac]Ac-J591for Progressive mCRPC	Active non recruting, estimated completion 2027-06	mCRPC treated with prior ARPI	Weill Medical College of Cornell University	Phase I/II
NCT03932318	Ac-225	[^{225}Ac]Ac-Lintuzumab	Venetoclax, Azacitidine, and [^{225}Ac]Ac-Lintuzumab in AML Patients	WITHDRAWN	Acute Myeloid LeukemiaRelapsed Adult AML	Actinium Pharmaceuticals	Phase I/II
NCT03867682	Ac-225	[^{225}Ac]Ac-Lintuzumab	Venetoclax and [^{225}Ac]Ac-Lintuzumab in AML Patients	Unknown status	Relapsed/refractory AML	Actinium Pharmaceuticals	Phase I/II
NCT03746431	Ac-225	[^{225}Ac]Ac-FPI-1434	A Phase 1/2 Study of [^{225}Ac]AcFPI-1434 Injection	Ongoing, estimated completion 2026-06	IGF-1R-positive solid tumours refractory to standard therapies	Fusion Pharmaceuticals	Phase I/II
NCT03705858	Ac-225	[^{225}Ac]Ac-Lintuzumab	[^{225}Ac]Ac -Lintuzumab in Patients With Acute Myeloid Leukemia	WITHDRAWN	Acute Myeloid Leukemia	Joseph Jurcic, Columbia University	Phase I
NCT03441048	Ac-225	[^{225}Ac]Ac-Lintuzumab	[^{225}Ac]Ac-Lintuzumab in Combination with Cladribine + Cytarabine + Filgastrim + Mitoxantrone (CLAG-M) for	Completed; 2024-05	Acute Myeloid Leukemia	Medical College of Wisconsin	Phase I

			Relapsed/Refractory Acute Myeloid Leukemia				
NCT03276572	Ac-225	[^{225}Ac]Ac-J591	Phase I Trial of [^{225}Ac]Ac-J591 in Patients With mCRPC	Completed with results, 2023-09	mCRPC treated with prior ARPI	Weill Medical College of Cornell University	Phase I
NCT02998047	Ac-225	[^{225}Ac]Ac-Lintuzumab	A Phase I Study of [^{225}Ac]Ac-Lintuzumab in Patients With Refractory Multiple Myeloma	Terminated, 2020-05	Refractory Multiple Myeloma	Actinium Pharmaceuticals	Phase I
NCT00672165	Ac-225	[^{225}Ac]Ac-Lintuzumab	Targeted Atomic Nano-Generators (Actinium-225-Labeled Humanised Anti-CD33 Monoclonal Antibody HuM195) in Patients With Advanced Myeloid Malignancies	Completed, 2015-02	Leukemia, Myelodisplastic syndrome	Memorial Sloan Kettering Cancer Center	Phase I
NCT00014495	Bi-213	[213Bi]Bi-Lintuzumab-(Bi213 MOAB M195)	Chemotherapy and Monoclonal Antibody Therapy in Treating Patients With Advanced Myeloid Cancer	Completed, 2009-12	LeukemiaMyelodysplastic SyndromesMyelodysplastic/Myeloproliferative Neoplasms	Memorial Sloan Kettering Cancer Center	Phase I/II
NCT06441994	At-211	PSW-1025 ([^{211}At]At-PSMA-5)	Clinical Trial of Targeted Alpha Therapy Using [^{211}At]At-PSMA-5] for Prostate Cancer	Ongoing, estimated completion 2027-03	Prostate Cancer	Osaka University	Phase I
NCT05275946	At-211	TAH-1005 ([^{211}At] NaAt)	Targeted Alpha Therapy Using Astatine-211 Against Differentiated Thyroid Cancer	Completed, 2025-03	Thyroid Cancer	Osaka University	Phase I

NCT04579523	At-211	[^{211}At]At -OKT10-B10	[^{211}At]At -OKT10-B10and Fludarabine Alone or in Combination With Cyclophosphamide and Low-Dose TBI Before Donor Stem Cell Transplant for the Treatment of Newly Diagnosed, Recurrent, or Refractory High-Risk Multiple Myeloma	Not yet recruting, estimated completion 2028-12	Multiple Myeloma|Recurrent Multiple Myeloma|Refractory Multiple Myeloma	Fred Hutchinson Cancer Center	Phase I
NCT04466475	At-211	[^{211}At]At-OKT10-B10	Radioimmunotherapy [^{211}At]At -OKT10-B10 and Chemotherapy (Melphalan) Before Stem Cell Transplantation for the Treatment of Multiple Myeloma	WITHDRAWN	Plasma Cell Myeloma	Fred Hutchinson Cancer Center	Phase I
NCT04461457	At-211	[^{211}At]At-MX35 F(ab')2	Targeted Radiation Therapy for Ovarian Cancer: Intraperitoneal Treatment With [^{211}At]At-MX35 F(ab')2	Completed, 2012-01	Ovarian Cancer	Vastra Gotaland Region	Early Phase I
NCT04083183	At-211	[^{211}At]At-BC8-B10 Monoclonal Antibody	Total Body Irradiation and [^{211}At]At-BC8-B10 Monoclonal Antibody for the Treatment of Nonmalignant Diseases	Ongoing, estimated completion 2028-01	Non-Malignant Neoplasm	Fred Hutchinson Cancer Center	Phase I/II
NCT03670966	At-211	[^{211}At]At-BC8-B10	[^{211}At]At-BC8-B10 Followed by Donor Stem Cell Transplant in Treating Patients With Relapsed or Refractory High-Risk Acute Leukemia or Myelodysplastic Syndrome	Ongoing, estimated completion 2029-03	hematology plan	Fred Hutchinson Cancer Center	Phase I/II

NCT00003461	At-211	[^{211}At]At-monoclonal antibody 81C6	Radiolabeled Monoclonal Antibody Therapy in Treating Patients With Primary or Metastatic Brain Tumours	Completed, 2005-02	Brain and Central Nervous System TumoursMetastatic CancerNeuroblastoma	Duke University	Phase I/II
NCT06710756	Pb-212	[^{212}Pb]Pb-At PSV359	[^{212}Pb]Pb-At PSV359 Therapy for Patients With Solid Tumours	Ongoing, estimated completion 2032-05	Pancreatic Ductal AdenocarcinomaGastric CancerEsophageal CancerColorectal CancerOvarian CancerHead and Neck Cancer	Perspective Therapeutics	Phase I/II
NCT06479811	Pb-212	[^{203}Pb]Pb-VMT-alpha-NET; [^{212}Pb]Pb-VMT-alpha-NET	[^{212}Pb]Pb-VMT-Alpha-NET in Metastatic or Inoperable Somatostatin-Receptor Positive Gastrointestinal Neuroendocrine Tumours, Pheochromocytoma/Paragangliomas, Small Cell Lung, Renal Cell, and Head and Neck Cancers	Not yet recruting, estimated completion 2032-01	Head and Neck TumoursKidney CancersSmall Cell Lung CancersPheochromocytoma/ParagangliomasGastrointestinal Neuroendocrine TumoursSomatostatin Receptor Positive	National Cancer Institute (NCI)	Phase I
NCT06427798	Pb-212	[^{203}Pb]Pb-VMT-alpha-NET; [^{212}Pb]Pb]VMT-alpha-NET	Somatostatin-Receptors (SSTR)-Agonist [^{212}Pb]Pb-VMT-alpha-NET in Metastatic or Inoperable SSTR+ Gastrointestinal Neuroendocrine Tumour and Pheochromocytoma/Paraganglioma Previously Treated With	Ongoing, estimated completion 2039-07	Somatostatin Receptor PositiveGastrointestinal Neuroendocrine TumoursPheochromocytomaParagangliomas	National Cancer Institute (NCI)	Phase I/II

			Systemic Targeted Radioligand Therapy				
NCT06148636	Pb-212	[^{212}Pb]Pb-VMT-alpha-NET; [^{212}Pb]Pb-VMT-alpha-NET	A Safety Study of [^{212}Pb]Pb-VMT-alpha-NET in Patients With Neuroendocrine Tumours	Active not recruting, estimated completion 2027-11	Neuroendocrine Tumours	David Bushnell	Early Phase I
NCT05725070	Pb-212	[^{212}Pb]Pb -NG001	Phase 0/1 Study of [^{212}Pb]Pb -NG001 in mCRPC	Completed, 2023-07	Metastatic Castration-resistant Prostate Cancer	ARTBIO Inc.	Early Phase I
NCT05720130	Pb-212	[^{212}Pb]Pb-ADVC001	Phase Ib/IIa Dose Escalation and Expansion Study of [^{212}Pb]Pb-ADVC001 in Metastatic Castration Resistant Prostate Cancer (TheraPb - Phase I/II Study).	Ongoing, estimated completion 2029-12	mCRPC with prior ARPI and no prior exposure to 177Lu	AdvanCell Pty Limited	Phase I/II
NCT05655312	Pb-212	[^{203}Pb]Pb-VMT01; [^{212}Pb]Pb-VMT01	MC1R-targeted Alpha-particle Monotherapy and Combination Therapy Trial With Nivolumab in Adults With Advanced Melanoma	Ongoing, estimated completion 2029-12	Melanoma	Perspective Therapeutics	Phase I/II
NCT05636618	Pb-212	[212Pb]VMT-α-NET; [212Pb]VMT-α-NET	Targeted Alpha-Particle Therapy for Advanced SSTR2 Positive Neuroendocrine Tumours	Ongoing, estimated completion 2029-12	Metastatic Castration-resistant Prostate Cancer	Perspective Therapeutics	Phase I/II
NCT05557708	Pb-212	[^{203}Pb]Pb-Pentixather; [^{212}Pb]Pb-Pentixather	A Safety Study of [^{212}Pb]Pb-Pentixather Radioligand Therapy	Not yet recruting, estimated completion 2030-06	Carcinoid Tumour LungNeuroendocrine Tumour of the LungCarcinoma, Small-Cell Lung	Yusuf Menda	Early Phase I

NCT05283330	Pb-212	[^{212}Pb]Pb-DOTAM-GRPR1	Safety and Tolerability of [^{212}Pb]Pb-DOTAM-GRPR1 in Adult Subjects With Recurrent or Metastatic GRPR-expressing Tumours	Ongoing, estimated completion 2027-08	GRPR1-positive solid tumours refractory to standard therapies	Orano Med LLC	Phase I
NCT05153772	Pb-212	[^{212}Pb]Pb-DOTAMTATE	Targeted Alpha-emitter Therapy of PRRT Naïve and Previous PRRT Neuroendocrine Tumour Patients	Active not recruting, estimated completion 2028-10	Neuroendocrine Tumours	Orano Med LLC	Phase II
NCT03466216	Pb-212	[^{212}Pb]Pb-DOTAMTATE	Phase 1 Study of AlphaMedix™ in Adult Subjects With SSTR (+) NET	Terminated, 2023-04	SSTR2-positive neuroendocrine tumours refractory to standard therapies	Radiomedix and Orano Med	Phase I
NCT01384253	Pb-212	[^{212}Pb]Pb-TCMC-Trastuzumab	Safety Study of [^{212}PbPb -TCMC-Trastuzumab Radio Immunotherapy	Completed, 2016-07	Breast NeoplasmsPeritoneal NeoplasmsOvarian NeoplasmsPancreatic NeoplasmsStomach Neoplasms	Orano Med LLC	Phase I
NCT05924672	Ra-223	[^{223}Ra]$RaCl_2$	Efficacy of Radium-223 in PSMA PET Optimally Selected Patients	Ongoing, estimated completion 2028-05	Castration-Resistant Prostate Carcinoma|Metastatic Malignant Neoplasm in the Bone|Stage IVB Prostate Cancer AJCC v8	University of California, San Francisco	Phase II

NCT05301062	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	A Research Called CREDIT Studies How Safe the Study Treatment Radium-223 is and How Well it Works in Chinese Men With Advanced Prostate Cancer That Has Spread to the Bones and Does Not Respond to Treatments for Lowering Testosterone Levels	Terminated, 2023-06	Metastatic Castration-resistant Prostate Cancer; Bone Metastases	Bayer	observational
NCT05133440	Ra-223	[^{223}Ra]RaCl$_2$	A Study of Stereotactic Body Radiation Therapy and [^{223}Ra]RaCl$_2$ in Prostate Cancer That Has Spread to the Bones	Active not recruting, estimated completion 2027-11	Prostate Cancer	Memorial Sloan Kettering Cancer Center	Phase II
NCT04681144	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	A Study to Learn More About How Radium-223 Affects the Quality of Life of Colombian Patients With Prostate Cancer That Has Not Responded to Testosterone Lowering Treatment and Has Spread to the Bones, and to Better Understand Its Safety	Completed, 2022-11	Prostate Cancer	Bayer	observational
NCT04597125	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Investigation of [^{223}Ra]RaCl$_2$ (Xofigo), a Treatment That Gives Off Radiation That Helps Kill Cancer Cells, Compared to a Treatment That Inactivates	Active not recruting, estimated completion 2026-10	Metastatic Castrate Resistant Prostate Cancer (mCRPC)	Bayer	Phase IV

			Hormones (New Antihormonal Therapy, NAH) in Patients With Prostate Cancer That Has Spread to the Bone Getting Worse on or After Earlier NAH				
NCT04587427	Ra-223	[^{223}Ra]$RaCl_2$	A Study to Learn More About How Radium-223 is Being Used With Other Treatments in European Patients Who Have Not Received Radium-223 Before	Completed, 2023-05	Bone Metastatic Castration-resistant Prostate Cancer	Bayer	observational
NCT04521361	Ra-223	[^{223}Ra]$RaCl_2$ (BAY88-8223)	A Study to Assess How Radium-223 Distributes in the Body of Patients With Prostate Cancer Which Spread to the Bones	Active not recruting, estimated completion 2025-09	Bone Metastatic Castration-resistant Prostate Cancer	Bayer	Phase I
NCT04516161	Ra-223	[^{223}Ra]$RaCl_2$ (BAY88-8223)	EPIX, a Study to Gather More Information About Characteristics of Patients and Other Factors Which May Contribute to Survival Over a Long Period of Time in Patients With Metastatic Castration-resistant Prostate Cancer (mCRPC) Treated With Radium-223 (Xofigo)	Completed, 2021-03	Metastatic Castration Resistant Prostate Cancer (mCRPC)	Bayer	observational
NCT04489719	Ra-223	[^{223}Ra]$RaCl_2$	Impact of DNA Repair Pathway Alterations on Sensitivity to	Ongoing, estimated completion 2029-08	Castration-Resistant Prostate Carcinoma;	University of Washington	observational

			Radium-223 in Bone Metastatic Castration-resistant Prostate Cancer		Metastatic Malignant Neoplasm in the Bone		
NCT04281147	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Study to Gather Information About the Use of Healthcare Services and the Way the Disease is Cared for in Canadian Patients With Prostate Gland Cancer Which Spread Throughout the Body	Completed, 2021-06	Prostate Cancer	Bayer	observational
NCT04256993	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	PRECISE, a Study to Gather More Information About Bone Fractures and Survival in Castration-resistant Prostate Cancer (CRPC) patients Treated With Radium-223 in Routine Clinical practIce in SwedEn	Completed, 2021-06	Metastatic Castration-Resistant Prostate Cancer	Bayer	observational
NCT04237584	Ra-223	[^{223}Ra]RaCl$_2$	A Study Comparing ARB With Radium-223 vs ARB Therapy With Placebo and the Effect Upon Survival for mCRPC Patients	Terminated, 2022-03	Metastatic Castration-resistant Prostate Cancer	MANA RBM	Phase III
NCT04232761	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Study to Gather Information on the Safety and How [^{223}Ra]RaCl$_2$, an Alpha Particle-emitting Radioactive Agent, Works Under Routine Clinical Practice in Taiwan in Patients	Completed, 2024-04	Castration-resistant Prostate Cancer	Bayer	observational

			With Castration-resistant Prostate Cancer (CRPC) Which Has Spread to the Bone				
NCT04110782	Ra-223	[^{223}Ra]RaCl$_2$	Radical Prostatectomy and External Beam Radiotherapy in mCRPC With [^{223}Ra]RaCl$_2$ (RaProRad)	UNKNOWN	Prostate Cancer	Azienda Policlinico Umberto I	observational
NCT04090398	Ra-223	[^{223}Ra]RaCl$_2$	Testing the Addition of Radium Therapy ([^{223}Ra]RaCl$_2$) to the Usual Chemotherapy Treatment (Paclitaxel) for Advanced Breast Cancer That Has Spread to the Bones	Active not recruting, estimated completion 2026-06	Anatomic Stage IV Breast Cancer; Metastatic HER2-Negative Breast Carcinoma; Metastatic Malignant Neoplasm in the Bone	National Cancer Institute (NCI)	Phase II
NCT04071236	Ra-223	[^{223}Ra]RaCl$_2$	Radiation Medication ([^{223}Ra]RaCl$_2$) Versus [^{223}Ra]RaCl$_2$ Plus Radiation Enhancing Medication (M3814) Versus [^{223}Ra]RaCl$_2$ M3814 Plus Avelumab (a Type of Immunotherapy) for Advanced Prostate Cancer Not Responsive to Hormonal Therapy	Ongoing, estimated completion 2026-04	Metastatic Castration-Resistant Prostate Carcinoma; Metastatic Malignant Neoplasm in the Bone; Metastatic Malignant Neoplasm in the Lymph Nodes; Stage IVB Prostate Cancer	National Cancer Institute (NCI)	Phase I/II
NCT04071223	Ra-223	[^{223}Ra]RaCl$_2$	Testing the Addition of a New Anti-cancer Drug, [^{223}Ra]RaCl$_2$, to the Usual Treatment (Cabozantinib) for Advanced Renal Cell Cancer That Has	Ongoing, estimated completion 2025-10	Advanced Renal Cell Carcinoma; Chromophobe Renal Cell Carcinoma; Clear Cell Renal Cell Carcinoma; Collecting Duct Carcinoma; Kidney	National Cancer Institute (NCI)	Phase II

			Spread to the Bone, RadiCaL Study		Medullary Carcinoma; Metastatic Malignant Neoplasm in the Bone; Papillary Renal Cell Carcinoma|Stage IV Renal Cell Cancer; Unclassified Renal Cell Carcinoma		
NCT03996473	Ra-223	[^{223}Ra]$RaCl_2$ (BAY88-8223)	Study to Test the Safety and How [^{223}Ra]$RaCl_2$ an Alpha Particle-emitting Radioactive Agent Works in Combination With Pembrolizumab an Immune Checkpoint Inhibitor in Patients With Stage IV Non-small Cell Lung Cancer With Bone Metastases	Terminated, 2023-01	Carcinoma, Non-Small-Cell Lung	Bayer	Phase I
NCT03903835	Ra-223	[^{223}Ra]$RaCl_2$	ProBio: A Biomarker Driven Study in Patients With Metastatic Prostate Cancer	Ongoing, estimated completion 2026-12	Metastatic Castration-resistant Prostate Cancer (mCRPC); Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)	Karolinska Institutet	Phase III
NCT03896984	Ra-223	[^{223}Ra]$RaCl_2$ (BAY88-8223)	Descriptive Analysis of Clinical Outcomes in Patients With Prostate Gland Cancer, Which Spreads to Other Parts of the Body, Who Were Treated First With Novel Anti-hormone Therapy Followed by a Second	Completed, 2020-12	Metastatic Castration-resistant Prostate Cancer (mCRPC)	Bayer	observational

			Line Treatment With Novel Anti-Hormone Therapy or RadIum-223 (Xofigo).				
NCT03737370	Ra-223	[^{223}Ra]RaCl$_2$	Fractionated Docetaxel and Radium-223 in Metastatic Castration-Resistant Prostate Cancer	Active not recruting, estimated completion 2026-12	Metastatic Castrate Resistant Prostate Cancer	Tufts Medical Center	Phase I
NCT03563014	Ra-223	[^{223}Ra]RaCl$_2$ (Xofigo, Bay88-8223)	A Local Retrospective Observational Study to Evaluate the Treatment Patterns of mCRPC Patients in Belgium Treated With Radium-223	Completed, 2019-01	Prostatic Neoplasms, Castration-Resistant	Bayer	observational
NCT03458559	Ra-223	[^{223}Ra]RaCl$_2$	Rhenium-188-HEDP vs. [^{223}Ra]RaCl$_2$ in Patients With Advanced Prostate Cancer Refractory to Hormonal Therapy	UNKNOWN	Prostate Cancer Metastatic to Bone	Amsterdam UMC, location VUmc	Phase III
NCT03419442	Ra-223	[^{223}Ra]RaCl$_2$	Multi-academic Center Study of Xofigo Patients	Completed, 2019-10	Prostate Cancer, Castration Resistant	Bayer	observational
NCT03368989	Ra-223	[^{223}Ra]RaCl$_2$	The Effects of [^{223}Ra]RaCl$_2$ Therapy on Radionuclide Bone Scan Lesions.	Completed, 2017-02	Bony Metastases From Castrate Refractory Prostate Cancer	The University of Texas Health Science Center, Houston	observational

NCT03361735	Ra-223	[^{223}Ra]$RaCl_2$	Radium [^{223}Ra]$RaCl_2$, Hormone Therapy and Stereotactic Body Radiation Therapy in Treating Patients With Metastatic Prostate Cancer	Active not recruting, estimated completion 2026-02	Prostate Adenocarcinoma	City of Hope Medical Center	Phase II
NCT03344211	Ra-223	[^{223}Ra]$RaCl_2$	Enzalutamide With or Without [^{223}Ra]$RaCl_2$ in Patients With Metastatic, Castration-Resistant Prostate Cancer	Active not recruting, estimated completion 2025-11	Bone Metastatic Castration-resistant Prostate Cancer	University of Southern California	Phase II
NCT03325127	Ra-223	[^{223}Ra]$RaCl_2$	Outcomes of mCRPC Patients Treated With Radium-223 Concomitant With Abiraterone or Enzalutamide- A Chart Review Study	WITHDRAWN	Prostatic Neoplasms, Castration-Resistant	Bayer	observational
NCT03317392	Ra-223	[^{223}Ra]$RaCl_2$	Testing the Safety of Different Doses of Olaparib Given Radium-223 for Men With Advanced Prostate Cancer With Bone Metastasis	Active not recruting, estimated completion 2026-04	Castration-Resistant Prostate Carcinoma; Metastatic Prostate Adenocarcinoma	National Cancer Institute (NCI)	Phase I/II
NCT03315260	Ra-223	[^{223}Ra]$RaCl_2$ (BAY88-8223)	Treatment Satisfaction With Radium-223 in Japan	Completed, 2023-03	Prostatic Neoplasms	Bayer	observational
NCT03304418	Ra-223	[^{223}Ra]$RaCl_2$	Radium-223 and Radiotherapy in Hormone-Naïve Men With Oligometastatic Prostate Cancer to Bone	Completed, 2023-08	Prostate Cancer Metastatic to Bone	University of Utah	Phase II
NCT03223597	Ra-223	[^{223}Ra]$RaCl_2$	Registry of Treatment Outcomes of Symptomatic	Completed, 2018-03	Prostate Cancer Metastatic; Bone Metastases	The Netherlands	observational

			Metastasized Castration Resistant Prostate Cancer Treated With Radium-223			Cancer Institute	
NCT03093428	Ra-223	[^{223}Ra]RaCl$_2$	Study Evaluating the Addition of Pembrolizumab to Radium-223 in mCRPC	Completed, 2025-02	Prostate Cancer	Dana-Farber Cancer Institute	Phase II
NCT03076203	Ra-223	[^{223}Ra]RaCl$_2$	Phase IB Trial of Radium-223 and Niraparib in Patients With Castrate Resistant Prostate Cancer (NiraRad)	Completed, 2022-11	Bone-only Metastatic Castration-Resistant Prostate Cancer (CRPC)	Sidney Kimmel Cancer Center at Thomas Jefferson University	Phase I
NCT03062254	Ra-223	[^{223}Ra]RaCl$_2$	Metabolic Change in Prostate Cancer Bone Metastases on [^{68}Ga]Ga-HBED-CC-PSMA PET/CT Following Radium-223 Therapy	Completed, 2021-07	Prostate Cancer	Sir Mortimer B. Davis - Jewish General Hospital	Phase II
NCT02928029	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Study Testing [^{223}Ra]RaCl$_2$ in Relapsed Multiple Myeloma	Terminated, 2019-03	Multiple Myeloma	Bayer	Phase I/II
NCT02925702	Ra-223	[^{223}Ra]RaCl$_2$ 55mBq/Kg every 4 weeks intravenously	PRORADIUM: Prospective Multi-centre Study of Prognostic Factors in mCRPC Patients Treated With Radium-223.	UNKNOWN	Advanced Prostate Cancer|Castration Resistant	Centro Nacional de Investigaciones Oncologicas CARLOS III	observational

NCT02903160	Ra-223	[^{223}Ra]RaCl$_2$	Prostate Cancer Intensive, Non-Cross Reactive Therapy (PRINT) for Castration Resistant Prostate Cancer (CRPC)	Completed, 2021-11	Prostate Cancer	Icahn School of Medicine at Mount Sinai	Phase II
NCT02899104	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Navigant Study- Treatment Patterns in mCRPC (Metastatic Castrate Resistant Prostate Cancer)	Completed, 2019-03	Prostatic Neoplasms, Castration-Resistant	Bayer	observational
NCT02880943	Ra-223	[^{223}Ra]RaCl$_2$	Dose-finding, Safety and Efficacy Study of [^{223}Ra]RaCl$_2$ (XOFIGO) in RCC Patients With Bone Metastases. (EIFFEL)	UNKNOWN	Clear-cell Metastatic Renal Cell Carcinoma; Bone Metastases	Association Pour La Recherche des Thérapeutiques Innovantes en Cancérologie	Phase I/II
NCT02814669	Ra-223	[^{223}Ra]RaCl$_2$	Safety and Tolerability of Atezolizumab (ATZ) in Combination With [^{223}Ra]RaCl$_2$ (R-223-D) in Metastatic Castrate-Resistant Prostate Cancer (CRPC) Progressed Following Treatment With an Androgen Pathway Inhibitor	Completed, 2019-07	Castrate-Resistant Prostate Cancer	Hoffmann-La Roche	Phase I
NCT02803437	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Drug Use Investigation of Xofigo, Castration Resistant	Completed, 2024-12	Prostatic Neoplasms, Castration-Resistant	Bayer	observational

			Prostate Cancer With Bone Metastases				
NCT02729103	Ra-223	[^{223}Ra]RaCl$_2$	Treatment Patterns in Metastatic Prostate Cancer	Completed, 2017-01	Prostatic Neoplasm	Bayer	observational
NCT02656563	Ra-223	[^{223}Ra]RaCl$_2$	Radium-223 Following Intermittent ADT	WITHDRAWN	Prostate Cancer	Canadian Urology Research Consortium	Phase II
NCT02605356	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Phase 1b/2 Study Testing [^{223}Ra]RaCl$_2$/Bortezomib/Dexamethasone Combination in Relapsed Multiple Myeloma	WITHDRAWN	Multiple Myeloma	Bayer	Phase I/II
NCT02582749	Ra-223	[^{223}Ra]RaCl$_2$	Androgen Deprivation Therapy +/- [^{223}Ra]RaCl$_2$ in Metastatic Prostate Cancer With Bone Metastases	Terminated, 2017-09	Prostate Cancer|Bone Metastases|Prostate Neoplasms	Ajjai Alva, MD	Phase II
NCT02518698	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Treatment Patterns in Castrate Resistant Prostate Cancer Patients With Bone Metastases in a Medicare Population	Completed, 2017-09	Prostate Cancer	Bayer	observational
NCT02507570	Ra-223	[^{223}Ra]RaCl$_2$	Open Label Phase Two Study of Enzalutamide With Concurrent Administration of [^{223}Ra]RaCl$_2$ in Castration-Resistant (Hormone-Refractory) Prostate Cancer Subjects With Symptomatic Bone Metastasis	Completed, 2019-01	Prostate Carcinoma Metastatic to the Bone	Carolina Research Professionals, LLC	Phase II

NCT02484339	Ra-223	[^{223}Ra]RaCl$_2$	Treatment of Advanced Castration Resistant Prostate Carcinoma With Limited Bone Metastases (α-RT)	UNKNOWN	Prostate Carcinoma	University Hospital Freiburg	Phase II
NCT02463799	Ra-223	[^{223}Ra]RaCl$_2$	Study of Sipuleucel-T W/ or W/O Radium-223 in Men With Asymptomatic or Minimally Symptomatic Bone-MCRPC	Completed, 2019-12	Prostate Cancer	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	Phase II
NCT02450812	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Non-interventional Study With Ra-223 Dichloride Assessing Overall Survival and Effectiveness Predictors for mCRPC Patients in a Real Life Setting in Germany	Completed, 2020-09	Prostatic Neoplasms, Castration-Resistant	Bayer	observational
NCT02442063	Ra-223	[^{223}Ra]RaCl$_2$	Phase Ib Study of Radium Ra 223 Dichloride in Combination With Paclitaxel in Cancer Subjects With Bone Lesions	Completed, 2016-10	Neoplasms;Bone Diseases	Bayer	Phase I
NCT02406521	Ra-223	[^{223}Ra]RaCl$_2$	Exploratory Study of Radium-223 and VEGF-Targeted Therapy in Patients With Metastatic Renal Cell Carcinoma and Bone Mets	Completed, 2019-12	Metastatic Renal Cell Carcinoma	Dana-Farber Cancer Institute	Phase I

NCT02398526	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Pain Evaluation in Radium-223 Treated Castration Resistant Prostate Cancer Patients With Bone Metastases	Completed, 2020-07	Castration-Resistant Prostatic Cancer	Bayer	observational
NCT02396368	Ra-223	[^{223}Ra]RaCl$_2$	A Study of Radium-223 in Combination With Tasquinimod in Bone-only Metastatic Castration-Resistant Prostate Cancer	WITHDRAWN	Bone-only Metastatic Castration-Resistant Prostate Cancer (CRPC)	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	Phase I
NCT02390934	Ra-223	[^{223}Ra]RaCl$_2$	Efficacy of Radium 223 in Radioactive Iodine Refractory Bone Metastases From Differentiated Thyroid Cancer	Completed, 2019-04	Thyroid Cancer	Gustave Roussy, Cancer Campus, Grand Paris	Phase II
NCT02366130	Ra-223	[^{223}Ra]RaCl$_2$	Trial of [^{223}Ra]RaCl$_2$ in Combination With Hormonal Therapy and Denosumab in the Treatment of Patients With Hormone-Positive Bone-Dominant Metastatic Breast Cancer	Completed, 2020-12	Breast Cancer	M.D. Anderson Cancer Center	Phase II
NCT02346526	Ra-223	[^{223}Ra]RaCl$_2$	A Biomarker Study of Standard-of-care [^{223}Ra]RaCl$_2$ for Metastatic Castration-resistant Prostate Cancer	Completed, 2020-12	Prostate Cancer; Castration-resistant Prostate Cancer; Castration-resistant	Massachusetts General Hospital	Phase II

					Prostate Cancer Metastatic to Bone		
NCT02331303	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	A Drug Utilization Study of Radium-223 in Sweden	Completed, 2017-12	Neoplasms	Bayer	observational
NCT02283749	Ra-223	[^{223}Ra]RaCl$_2$	BrUOG L301 With Non-Small Cell Lung Cancer and Bone Metastases	Completed, 2018-11	Non Small Cell Lung Cancer With Bone Metastatses	Angela Taber MD	Phase II
NCT02278055	Ra-223	[^{223}Ra]RaCl$_2$	Non-Randomized Trial Assessing Pain Efficacy With Radium-223 in Symptomatic Metastatic Castration-Resistant Prostate Cancer	Completed, 2022-02	Metastatic Prostate Cancer|Pain	Memorial Sloan Kettering Cancer Center	Phase II
NCT02258464	Ra-223	[^{223}Ra]RaCl$_2$	Study of [^{223}Ra]RaCl$_2$ Versus Placebo and Hormonal Treatment as Background Therapy in Subjects With Bone Predominant HER2 (Human Epidermal Growth Factor Receptor 2) Negative Hormone Receptor Positive Metastatic Breast Cancer	Terminated, 2019-08	Breast Neoplasms	Bayer	Phase II
NCT02258451	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Study of [^{223}Ra]RaCl$_2$ in Combination With Exemestane and Everolimus Versus Placebo in Combination With Exemestane and Everolimus in Subjects With Bone	Completed, 2022-10	Breast Neoplasms	Bayer	Phase II

			Predominant HER2 Negative Hormone Receptor Positive Metastatic Breast Cancer				
NCT02199197	Ra-223	[^{223}Ra]RaCl$_2$	Radium-223 With Enzalutamide Compared to Enzalutamide Alone in Men With Metastatic Castration Refractory Prostate Cancer	Completed, 2019-10	Prostate Cancer	University of Utah	Phase II
NCT02194842	Ra-223	[^{223}Ra]RaCl$_2$	Phase III Radium-223 mCRPC-PEACE III	Active not recruting, estimated completion 2028-12	Prostate Cancer	European Organisation for Research and Treatment of Cancer - EORTC	Phase III
NCT02141438	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Observational Study for the Evaluation of Long-term Safety of Radium-223 Used for the Treatment of Metastatic Castration Resistant Prostate Cancer	Completed, 2024-10	Metastatic Castration-resistant Prostate Cancer	Bayer	observational
NCT02135484	Ra-223	[^{223}Ra]RaCl$_2$ Alpharadin	Radium-223 in Castrate Resistant Prostate Cancer Bone Metastases	Completed, 2020-12	Prostate Cancer	M.D. Anderson Cancer Center	NA
NCT02097303	Ra-223	[^{223}Ra]RaCl$_2$	Open Label Phase Two Trial of [^{223}Ra]RaCl$_2$ With Concurrent	Completed, 2015-12	Prostate Cancer	Carolina Research	Phase II

			Administration of Abiraterone Acetate Plus Prednisone in Symptomatic Castration-Resistant (Hormone-Refractory) Prostate Cancer Subjects With Bone Metastasis			Professionals, LLC	
NCT02043678	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	[^{223}Ra]RaCl$_2$ and Abiraterone Acetate Compared to Placebo and Abiraterone Acetate for Men With Cancer of the Prostate When Medical or Surgical Castration Does Not Work and When the Cancer Has Spread to the Bone, Has Not Been Treated With Chemotherapy and is Causing no or Only Mild Symptoms	Completed, 2024-02	Prostatic Neoplasms	Bayer	Phase III
NCT02034552	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	A Randomized Phase IIa Efficacy and Safety Study of [^{223}Ra]RaCl$_2$ With Abiraterone Acetate or Enzalutamide in Metastatic Castration-resistant Prostate Cancer (CRPC)	Completed, 2018-06	Prostatic Neoplasms	Bayer	Phase II
NCT02023697	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Standard Dose Versus High Dose and Versus Extended Standard Dose [^{223}Ra]RaCl$_2$ in Castration-resistant Prostate Cancer Metastatic to the Bone	Completed, 2018-08	Prostatic Neoplasms	Bayer	Phase II

NCT01934790	Ra-223	[^{223}Ra]$RaCl_2$ (BAY88-8223)	Re-treatment Safety of [^{223}Ra]$RaCl_2$ in Castration-resistant Prostate Cancer With Bone Metastases	Completed, 2017-04	Prostatic Neoplasms	Bayer	Phase I/II
NCT01929655	Ra-223	[^{223}Ra]$RaCl_2$ (BAY88-8223)	Japanese BAY88-8223 Monotherapy Phase II Study	Completed, 2017-05	Prostatic Neoplasms	Bayer	Phase II
NCT01810770	Ra-223	[^{223}Ra]$RaCl_2$ (BAY88-8223)	[^{223}Ra]$RaCl_2$ Asian Population Study in the Treatment of CRPC Patients With Bone Metastasis	Completed, 2017-09	Prostatic Neoplasms	Bayer	Phase III
NCT01798108	Ra-223	[^{223}Ra]$RaCl_2$ (BAY88-8223)	Dose Escalation Study of [^{223}Ra]$RaCl_2$ in Patients With Advanced Skeletal Metastases	Completed, 2003-06	Neoplasm Metastasis	Bayer	Phase I
NCT01618370	Ra-223	[^{223}Ra]$RaCl_2$ (BAY88-8223)	[^{223}Ra]$RaCl_2$ (Alpharadin) in Castration-Resistant (Hormone-Refractory) Prostate Cancer Patients With Bone Metastases	Completed, 2016-02	Prostatic Neoplasms	Bayer	Phase III
NCT01565746	Ra-223	[^{223}Ra]$RaCl_2$ (BAY88-8223)	Safety, Biodistribution, Radiation Dosimetry and Pharmacokinetics Study of BAY88-8223 in Japanese Patients	Completed, 2016-04	Prostatic Neoplasms	Bayer	Phase I
NCT01106352	Ra-223	[^{223}Ra]$RaCl_2$ (Xofigo, BAY88-8223)|DRUG: Docetaxel	A Study of Alpharadin With Docetaxel in Patients With Bone Metastasis From Castration-Resistant Prostate Cancer (CRPC)	Completed, 2015-06	Bone Metastases|Castration-Resistant Prostate Cancer	Bayer	Phase I/II

NCT01070485	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	BAY88-8223, Alpharadin, Breast Cancer Patients With Bone Dominant Disease	Completed, 2012-01	Breast Cancer|Bone Metastases	Bayer	Phase II
NCT00748046	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	Alpharadin™ ([^{223}Ra]RaCl$_2$) Safety and Dosimetry With HRPC That Has Metastasized to the Skeleton	Completed, 2009-10	Prostate Cancer|Metastases|Pharmacokinetics	Bayer	Phase I
NCT00699751	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	A Phase III Study of [^{223}Ra]RaCl$_2$ in Patients With Symptomatic Hormone Refractory Prostate Cancer With Skeletal Metastases	Completed, 2014-02	Hormone Refractory Prostate Cancer|Bone Metastases	Bayer	Phase III
NCT00667537	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	PK in Pts With HRPC & Skeletal Metastes	Completed, 2008-12	Prostatic Neoplasms	Bayer	Phase I
NCT00667199	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	BAY88-8223, Does Response Study in HRPC Patients	Completed, 2009-10	Hormone Refractory Prostate Cancer; Bone Metastases	Bayer	Phase II
NCT00459654	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	A Placebo-controlled Phase II Study of Bone-targeted Radium-223 in Symptomatic Hormone-refractory Prostate Cancer	Completed, 2007-05	Prostate Cancer|Neoplasm Metastasis	Bayer	Phase II
NCT00337155	Ra-223	[^{223}Ra]RaCl$_2$ (BAY88-8223)	BAY88-8223, Dose Finding Study in Patients With HRPC	Completed, 2009-12	Prostate Cancer|Neoplasm Metastasis	Bayer	Phase II
NCT04147819	Th-227	BAY2701439	A First in Human Study of BAY2701439 to Look at Safety, How the Body Absorbs, Distributes and Excretes the Drug, and How Well the Drug	Completed, 2023-09	Cancers With HER2 Expression	Bayer	Phase I

			Works in Participants With Advanced Cancer Expressing the HER2 Protein				
NCT03724747	Th-227	BAY2315497	Study to Evaluate the Safety, Tolerability,Pharmacokinetics, and Antitumour Activity of a Thorium-227 Labeled Antibody-chelator Conjugate Alone and in Combination With Darolutamide, in Patients With Metastatic Castration Resistant Prostate Cancer	Completed, 2024-10	Metastatic Castration Resistant Prostate Cancer (mCRPC)	Bayer	Phase I
NCT03507452	Th-227	BAY2287411	First-in-human Study of BAY2287411 Injection, a Thorium-227 Labeled Antibody-chelator Conjugate, in Patients With Tumours Known to Express Mesothelin	Completed, 2022-03	Advanced Recurrent Malignant Pleural Epithelioid Mesothelioma; Advanced Recurrent Malignant Peritoneal Epithelioid Mesothelioma; Advanced Recurrent Serous Ovarian Cancer; Advanced Pancreatic Ductal Adenocarcinoma	Bayer	Phase I
NCT02581878	Th-227	BAY1862864	Safety and Tolerability of BAY1862864 Injection in Subjects With Relapsed or Refractory CD22-positive Non-Hodgkin's Lymphoma	Completed, 2019-11	Lymphoma, Non-Hodgkin	Bayer	Phase I

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