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STATUS OF CLINICAL ALPHATHERAPY

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The history of clinical alphatherapy

Clinical alpha therapy dates back several decades and began in the 1940s, mainly in Germany, with the intravenous injection of radium-224, an alpha particle emitter with a half-life of 3.6 days, in patients with hyperalgesic ankylosing spondylitis (1). Once incorporated into bone tissue, particularly in areas of increased renewal (inflamed joints and spinal areas in ankylosing spondylitis), this alpha radiation damages the DNA of nearby hyperactive immune and bone cells, thereby suppressing inflammation and bone remodeling and thus pain. The risks of oncological and, in particular, hematological complications were not a major concern for prescribers, even though they had been assessed decades earlier.

To assess this long-term oncological toxicity, a study compared toxicity in 1,471 patients treated with radium-224 between 1948 and 1975 and in 1,324 untreated patients during the same period (1). With a follow-up period of 25 and 26 years for the two groups, an excess of myeloid leukemia was statistically demonstrated with 7 cases observed versus 1.8 expected cases (P=0.003) in the treated group and 4 cases observed versus 3.1 expected cases in the control group. Following this publication, treatment with radium-224 was discontinued in 1985 for this indication of ankylosing spondylitis.

Twenty-eight years later, in 2013, the first radiopharmaceutical using radium-223 (half-life of 11.4 days), an alpha particle emitter (Xofigo®), was approved in the US and Europe for the treatment of metastatic prostate cancer, with a significant but modest overall survival benefit of 2.8 months (14.0 vs. 11.2) compared to the control group in a phase 3 study of 921 patients (2). Following its launch in the US and Europe in 2013, sales of this radiopharmaceutical increased until 2017 before declining significantly in subsequent years due to new, more effective radiopharmaceuticals using the electron-emitting lutetium-177.

A phase 3 study conducted with Lutetium-177-PSMA-617 (Pluvicto®) in 831 patients with metastatic prostate cancer showed a median overall survival of 15.3 months in the treated group compared to 11.3 months in the control group (4). Marketing authorization was obtained in Europe and the US in 2022, opening real prospects for the clinical development of Radioligand Therapy (RLT). Since these marketing authorizations, numerous clinical studies are underway with various vectors labeled with lutetium-177 in a variety of clinical indications.

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Alongside this rapid clinical development, interest has focused on the clinical development of the same vectors labeled with new-generation radioisotopes that emit alpha particles. The three radioisotopes currently under consideration are actinium-225, lead-212, and astatine-211. They share the key characteristic of emitting large alpha particles comprising two protons and two neutrons (helium nuclei) with a linear energy transfer 100 times higher than that of electrons emitted by lutetium-177. This results in a cytotoxic effect characterized by irreparable breaks in both strands of tumor cell DNA, leading to cell death, whereas the electrons emitted by lutetium-177 cause reparable breaks in one of the two strands of DNA. This is a decisive advantage of alpha particles over electrons emitted by lutetium-177.

In 2025, 28 phase 1 or 1/2 studies were registered on the US ClinicalTrials.gov database, including 14 with actinium-225, 6 with lead-212, and 8 with astatine-211.

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Actinium-225

The largest number of clinical studies have been conducted with actinium-225 due to its availability linked to its 10-day half-life, which allows it to be transported over long distances. Several industrial methods can be used to produce this radioisotope. It can be produced from thorium-229 generators, which is a daughter product of uranium-233 obtained during historical nuclear activities, but this production depends on the limited reserves of uranium-233 worldwide. It can also be produced in accelerators by bombarding radium-226 targets with gamma rays, but this production method presents risks of exposure to alpha and gamma rays from radium-226, which has a half-life of 1,600 years, and of internal contamination through inhalation or ingestion of the radon gas produced.

A dozen studies using Actinium-225 have been sponsored by seven major pharmaceutical companies (Fig.1). Most of these studies chose two clinical indications for which marketing authorization had been obtained with the same vector labeled with lutetium-177, an electron emitter, namely neuroendocrine tumors (5) and metastatic prostate cancer (6), anticipating superior therapeutic efficacy with actinium-225. With sufficient financial resources, phases 1 and 3 are underway with substantial numbers of patients. Finally, one company has chosen two indications and two vectors whose performance has not yet been validated with lutetium-177.

FIGURE 1 : INVOLVEMENT OF BIG PHARMA COMPANIES IN ALPHA-THERAPY WITH ACTINIUM-225

Big Pharmas	AstraZeneca (Fusion Phar)	Bayer	Bristol Myers Squibb (Rayze Bio)	J&J	Eli Lilly	Novartis
Chosen target(s)	IGF-1R EGFR c-MET	PSMA	SSTRs	Kallikrein 2	PSMA	PSMA
Radionuclide	Ac-225	Ac-225	Ac-225	Ac-225	Ac-225	Ac-225
Targeted Pathology	Solid tumors	Prostate cancer	Gastro-entero pancreatic Neuroendocrine tumors	Prostate cancer	Prostate cancer	Prostate cancer
Clinical Phase	Phase 1 NCT03746431 (253 pts) Phase 1 NCT06147037 (169 pts)	Phase 1 NCT06052306 (232 pts) Phase 1 NCT06217822 (235 pts)	Phase 3 NCT05477576 (288 pts)	Phase 1 NCT04644770 (247 pts)	Phase 1 NCT06229366 (142 pts)	Phase 3 NCT06854277 (605 pts)

Actinium-225 has also been chosen by 11 biotech companies for the development of phase 1 studies using targets already validated with lutetium-177 in two cases and six new targets (Fig. 2 a-b). The targeted clinical indications vary and include leukemia in five studies, melanoma in two studies, small cell lung cancer in two studies, solid tumors in general in two studies, and colorectal cancer and sarcomas in one study.

FIGURE 2A: INVOLVEMENT OF BIOTECH COMPANIES IN ALPHA-THERAPY USING 225AC

BioTech	Abdera Therapeutics	Aktis Oncology	Full-life Technologies	Modulation Therapeutics	Ariceum Therapeutics
Chosen target(s)	DLL3	Nectin 4	PSMA	Melanocortin-1 receptor	SSTR2
Radionuclide	Ac-225	Ac-225	Ac-225	Ac-225	Ac-225
Targeted Pathology	SCLC and NET	Solid Tumors	Prostate cancer	Uveal melanoma	SCLC
Clinical Phase	Phase 1 NCT06736418 (65 pts)	Phase 1 NCT07020117 (150 pts)	Phase 1 NCT06492122 (35 pts)	Phase 1 NCT05496686 (16 pts)	Phase 1/2 NCT06939036 (50 pts)

FIGURE 2B: INVOLVEMENT OF BIOTECH COMPANIES IN ALPHA-THERAPY USING 225AC

BioTech	Ratio Therapeutics	Alpha-9 Oncology	Precirix	Medical College Wisconsin	Actinium Pharmaceuticals	NCI	Actinium Pharmaceuticals	NCI
Chosen target(s)	FAP	MC1R CEA	FAP	Anti-CD33 + CLAG M	Anti-CD33 +Venetoclax	Anti-CD33 +Venetoclax +Decitabine +Cedazuridine	Anti-CD33	Anti-CD33
Radionuclide	Ac-225	Ac-225	Ac-225	Ac-225	Ac-225	Ac-225	Ac-225	Ac-225
Targeted Pathology	Aggressive Sarcomas	Melanoma Colorectal cancer	Solid tumors	RR AML	RR AML	Newly diagnosed AML	Older AML	High risk MDS
Clinical Phase	Phase 1 NCT07156565 (26 pts)	Phase 1 NCT07076550 (50 pts) Phase 1 NCT05204147 (20 pts)	Phase 1 Coming soon	Phase 1 NCT03441048 (26 pts)	Phase 1/2 NCT03867682 (38 pts)	Phase 1 NCT06802523 (53 pts)	Phase 1/2 NCT02575963 (40 pts)	Phase 1/2 NCT06888323 (30 pts)

Lead-212

Lead-212 is produced by industrial extraction of thorium-228 from thorium-232. The industrial process consists of a series of chemical extractions and purifications aimed at isolating first radium-228 and then thorium-228, whose decay successively produces radium-224 and then lead-212.

In 2025, six phase 1/2 clinical trials were registered on the Clinicaltrials.gov website with lead-212 (Figs. 1 and 3). Four of these target the PSMA and SSTR antigens, which were previously labeled with lutetium-177 (7) with favorable clinical results. One targets the MC1R (melanocortin receptor) antigen for the treatment of melanoma, and the other targets the GRPR (gastrin-releasing peptide receptor) antigen for the treatment of breast and prostate cancers.

FIGURE 3 : INVOLVEMENT OF BIOTECH COMPANIES IN ALPHA-THERAPY USING 212PB

Biotechs	AdvanCell	Artbio	Perspective Therapeutics	Oranomed	Sanofi (Orano Med)
Chosen target(s)	PSMA	PSMA	SSTR2 and MC1R	GRPR	SSTRs
Radionuclide	Pb-212	Pb-212	Pb-212	Pb-212	Pb-212
Targeted Pathology	Prostate cancer	Prostate cancer	Neuroendocrine tumors and melanomas	Breast prostate	Neuroendocrine tumors
Clinical Phase	Phase 1/2 NCT06590857 (100 pts)	Early Phase 1 NCT05725070 (3 pts)	Phase 1/2 NCT05636618 (260 pts) Phase 1/2 NCT05655312 (264 pts)	Phase 1 NCT05283330 (55 pts)	Phase 2 NCT05153772 (69 pts)

Astatine-211

Astatine-211 can be produced with a medium energy (30 MeV) cyclotron using a safe and cheap bismuth target. Astatine-211 is promising as it decays with 100% alpha particle emission and has no long-lived toxic daughter nuclides. Its rather short half-life (7.2 hrs) shows an advantage for public health but needs availability of a production site close to clinical center.

In 2025, eight phase 1/2 clinical trials were registered with astatine-211 (Fig. 4). The oldest study targeted tenascin for the treatment of glioblastomas (8). Three of them target the CD45 antigen, which is also targeted with actinium-225 for onco-hematological indications. One study targets the NIS symporter for the treatment of thyroid cancer refractory to iodine-131 therapy, and one study targets PSMA for the treatment of metastatic prostate cancer.

FIGURE 4 : INVOLVEMENT OF BIOTECH COMPANIES IN ALPHA-THERAPY USING 211AT

Biotechs	Duke University	Vastra Gotaland Region	Fred Hutchinson Cancer Center				Osaka University	
Chosen target(s)	Tenascin	NaPi2b (MX35)	CD 45	CD 45	CD 45	CD 38	NIS	PSMA
Radionuclide	At-211	At-211	At-211	At-211	At-211	At-211	At-211	At-211
Targeted Pathology	Primary or Metastatic brain tumors	Ovarian carcinoma	Acute Leukemias	Non-Malignant Neoplasm	High risk acute leukemias	High risk multiple myeloma	Thyroid Cancer	Prostate Cancer
Clinical Phase	Phase 1/2 NCT00003461 (18 pts)	Phase 1 NCT04461457 (12 pts)	Phase 1/2 NCT03128034 (30 pts)	Phase 1/2 NCT04083183 (40 pts)	Phase 1/2 NCT03670966 (30 pts)	Phase 1/2 NCT04579523 (30 pts)	Phase 1 NCT05275946 (12 pts)	Phase 1 NCT06441994 (15 pts)

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The prospects for alpha therapy

The crucial issue for the use of the three alpha particle emitters is their availability for clinical use. Industrial solutions are currently being developed for actinium-225 and lead-212. The same is true for astatine-211, which can be produced by a conventional cyclotron with a beam intensity capable of producing high activity levels for large-scale clinical use. The Belgian company IBA (Ion Beam Application), the world leader in the production and sale of cyclotrons for medical use, is currently developing a prototype industrial cyclotron with a beam intensity capable of producing the astatine-211 activity required to treat many patients. An agreement has been signed with Framatome for the acquisition of an initial pilot cyclotron located in Nantes, prior to acquiring a network of cyclotrons located in Europe and the US to cover the industrial-scale production of astatine-211.

In this context, the biotech company Atonco, based in Nantes-Saint-Herblain, conducted a clinical study using an anti-CAIX antibody licensed from the Australian company Telix Pharmaceuticals and labeled with zirconium-89 (9). This study confirmed the good retention of the labeled antibody in the bladder cavity after intravesical instillation and the absence of radioactivity extravasation outside the bladder. It also demonstrated the high tumor radio-cytotoxicity of astatine-211 compared to lutetium-177 using a tumor cell line expressing the CAIX antigen. It also enabled the next step to be taken in the Phase 1 FIH clinical study currently being planned.

In conclusion, radioligand therapy has recently become established in the therapeutic arsenal in oncology, and its use is rapidly increasing in both validated indications and in clinical evaluation for other indications. In the short and medium term, it could be supplemented by the use of new alpha-emitting radioisotopes, which have a much higher cytotoxic potential than electron-emitting radionuclides. However, their clinical performance has yet to be demonstrated in the numerous clinical studies currently underway. Once this performance has been confirmed, the radionuclides should be available once the manufacturing projects currently underway have been completed.

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