

Our history

In the early 2000s, Areva (now Orano) looked at opportunities to use material derived from its core nuclear energy activities. Nuclear medicine and Radioligand Therapy quickly appeared very promising. Lead-212 was identified as offering tangible scientific prospects, and Orano had the necessary know-how to meet the challenges involved in its procurement. With sufficient resources to produce lead-212 in larger quantities, the project soon launched to demonstrate the feasibility of extracting and purifying this isotope. Successful results from conclusive preclinical studies with the National Cancer Institute in the U.S. led to the creation of Orano Med in 2009.

Orano Med, a subsidiary of the Orano Group, is a clinical-stage biotechnology company developing a new generation of targeted therapies against cancer using the unique properties of lead-212 (^{212}Pb), a rare alpha-emitting radioisotope and one of the most potent therapeutic payloads against cancer cells.

Our mission

Orano Med seeks to develop a new generation of targeted therapies against cancer using the unique properties of lead-212, a rare alpha-emitting radioisotope and one of the most potent therapeutic payloads against cancer cells. Although oncology research has made tremendous progress in recent years, medical needs remain unmet for many types of cancer. Our approach, known as **Targeted Alpha Therapy (TAT)**, opens up promising prospects for patients not responding to existing treatments.

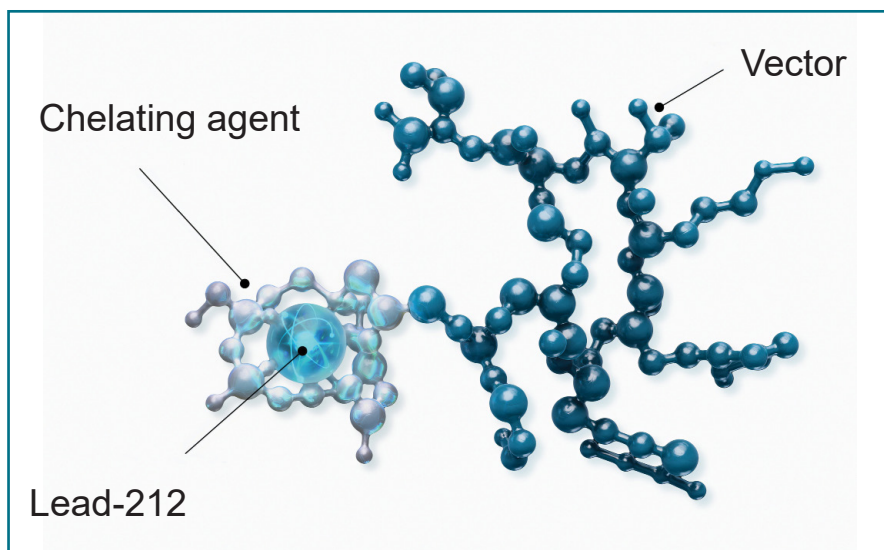
Our strategy

Orano Med's strategy has two goals:

- **developing a robust pipeline of lead-212-based therapies:** We focus our developments on areas of high unmet needs where lead-212 labeled compounds could make a difference and, since 2016, our preclinical facility in the United States (Plano, Texas) has accelerated the transition of our molecules into clinical research.
- **providing a reliable supply chain for these innovative drugs:** Because reliability of supply of alpha emitters has long hindered the development of TAT, we are also investing in our production facilities in France and in the United States. Our facilities currently have the capacity to supply all the lead-212 necessary to conduct clinical trials and we are ramping up to industrial production capacity to meet commercial needs.

Lead-212 Alpha Therapy

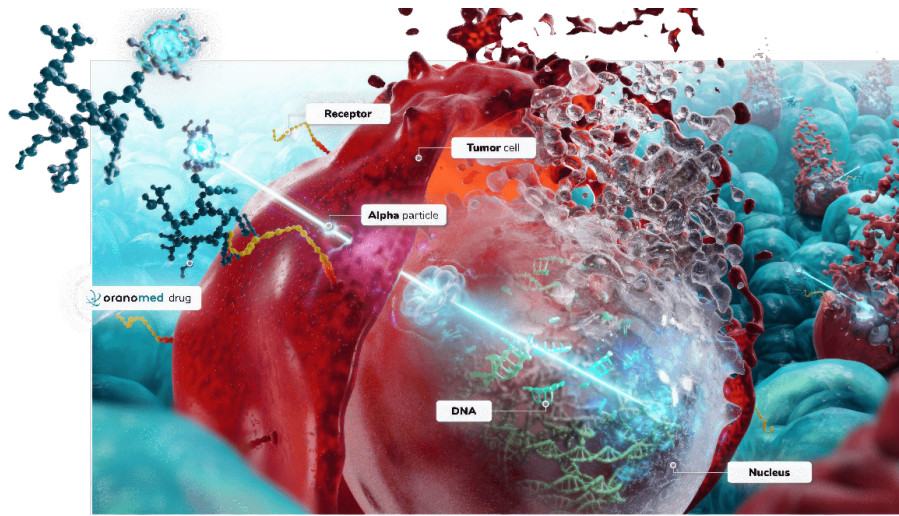
TARGETED ALPHA THERAPY : A powerful way to treat cancer



Targeted Alpha Therapy relies on a simple concept: combining the ability of biological molecules to target cancer cells with the short-range cell-killing capabilities of alpha-emitting radioisotopes.

The drugs developed by Orano Med consist of:

- an atom of lead-212, an in vivo generator of alpha emitters,
- a biological vector (peptide, antibody, etc.) specifically targeting tumor cells,
- a chelating agent to bind the lead-212 to the vector.



Lead-212 can be combined with a wide range of targeting vectors, thereby vastly increasing the potential range of applications in oncology.

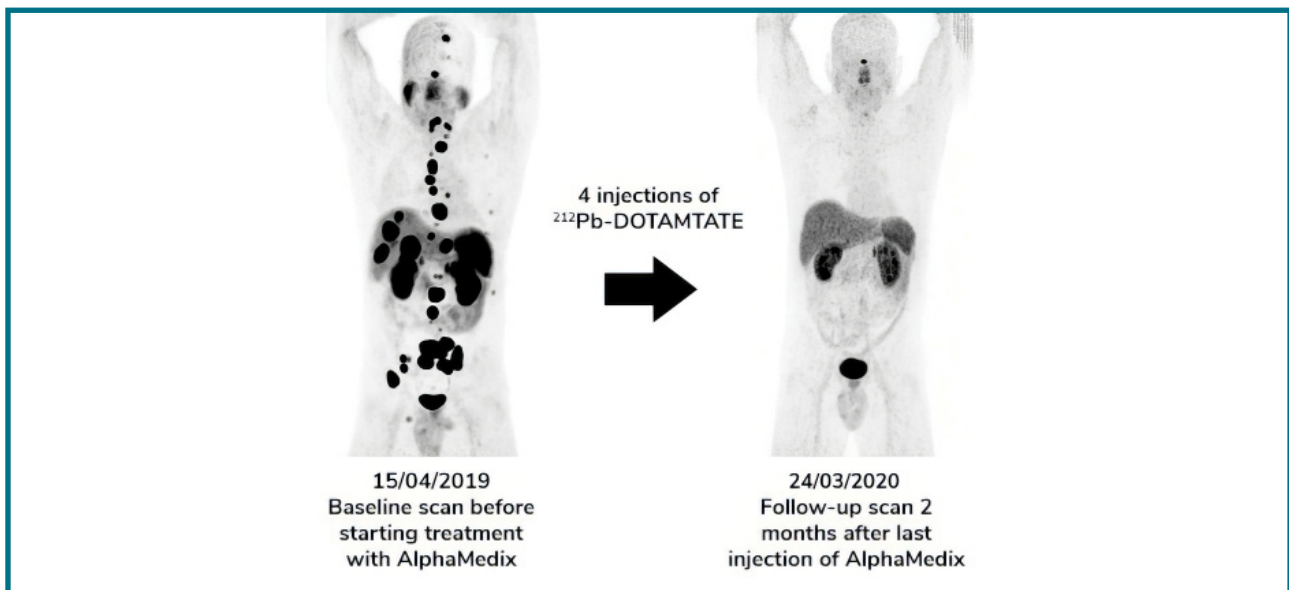
Superiority of targeted alpha therapy in the fight against cancer

Two types of isotopes can be used in radioligand therapies: emitters of alpha or beta radiation. Currently, only beta therapies are commercially available. However, alpha particles have **two key benefits** for applications in oncology:

1 - Improved biological efficacy

Alpha decay consists of the emission of a helium nucleus (alpha particle) together **with linear energy transfer which is 100 times higher than that of beta radiation**. The alpha radiation thus causes **irreparable double-strand breaks in the DNA** of cancer cells in immediate proximity to the emission while beta radiation has more of a tendency to cause single-strand breaks.

As a result, **alpha emitters** are considered as the most powerful payloads to be found for targeted therapies with fewer than five particles needed to kill a cancer cell versus hundreds of beta emitting isotopes or thousands of chemotherapy toxins.



Patient with metastatic neuroendocrine tumors included in the Phase 1 clinical trial of AlphaMedix (lead-212-DOTAMTATE), a drug currently being developed by Orano Med.

2 - Toxicity limited due to short range of emission

The alpha particles only travel **a very short distance into the tissue: only 2 to 5 cell layers** (compared to more than 50 with beta radiation). They thus deposit a very large amount of energy over a very short distance. This results in an increased cytotoxic potential toward cancer cells while **limiting toxicity to nearby healthy cells**.

Pipeline

Based on the unique properties of lead-212, Orano Med is developing a **multi-asset pipeline to combine lead-212 with diverse biological vectors** targeting or binding to different specific cancer receptors or antigens. Our pipeline is composed of a mix of partnered compounds and internal developments.

Program	Indication	Discovery	PoC	Pre-IND	Phase 1	Phase 2/3	Partner
AlphaMedix™	Neuroendocrine tumors						sanofi 
²¹² Pb-GRPR	Solid tumors (breast and prostate cancer)						oranomed 
²¹² Pb-PSMA	Prostate cancer						oranomed 
²¹² Pb CEA-PRIT	Solid tumors						Roche 
²¹² Pb - DARPIn-DLL3 / MP0712	Small-cell lung cancer						MOLECULAR partners 
²¹² Pb DARPIn-MSLN	Solid tumors (including ovarian cancer)						MOLECULAR partners 
²¹² Pb DARPIn	Undisclosed target						MOLECULAR partners 
²¹² Pb PRRT	Undisclosed target						Phage display platform 48Hour Discovery 
²¹² Pb PRRT	Undisclosed target						Phage display platform BIOSYNTH 
²¹² Pb PRRT	Several targets						Undisclosed
²¹² Pb TAT	Several targets						Undisclosed

Industrial platform

In order to produce lead-212-conjugated drugs and distribute them, Orano Med has developed a global industrial platform.

In France at Bessines-sur-Gartempe, the **Laboratoire Maurice Tubiana (LMT)** is implementing the upstream phase of the process: the production of radium-228 and thorium-228 from which the doses of ²¹²Pb will be extracted.

Still in Bessines-sur-Gartempe, a larger facility called **Advanced Thorium Extraction Facility (ATEF)** is under construction to industrialize the upstream phase of the process and meet global demand. It will be the world's first industrial facility dedicated to the production of thorium-228, the precursor to lead-212, for radioligand therapy applications. This project marks a major milestone in the availability of innovative cancer treatments. Covering an area of 7,000 m², ATEF is set to be operational in 2027 and will increase the current production capacity of the Maurice Tubiana laboratory by ten times.

In the USA at Plano in Texas, the **Drug Development & Preclinical Unit (DDPU)** produces ²¹²Pb for North America from precursors supplied by the LMT. It also manufactures drugs for clinical trials in accordance with GMP standards assembling the ²¹²Pb with the chelating agent and the targeting molecule.

In the USA at Brownsburg in Indiana, the first **Alpha Therapy Laboratory (ATLab)** is responsible for the large-scale production of ²¹²Pb radioligand therapies and their distribution in North America, from thorium-228 supplied by the LMT.

In France, an **ATLab is also under construction in Onnain**, near Valenciennes. Likewise, it will commence the large-scale production of ²¹²Pb radioligand therapies and their distribution in Europe as of 2025. Based on a modular design, further production lines may be added in the future to allow for the manufacturing and distribution of several drugs simultaneously.

Given the half-life of ²¹²Pb (10.6 hours), the drugs must be produced close to hospitals. The construction of other ATLabs are planned to cover global needs.