

Category

Best Startup

Product/Solution Name

Targeted Alphatherapy with Lead-212

Date of Approval

N/A

Indications

Wide range of applications in oncology for the targeted alphatherapy with lead-212 platform developed by Orano Med

Neuroendocrine tumors expressing somatostatin receptors for AlphaMedix

Therapeutic Categories

Oncology and Hematology

Background information and need for solution/product

Principles of RLT :

Although oncology research has made tremendous progress in recent years, there remains a high level of unmet medical need for many types of cancer, especially at metastatic stage. According to the World Health Organization, cancer accounted for nearly 10 million deaths in 2020.

The fight against cancer has witnessed significant advancements with the development of targeted therapies. Among them, Radioligand therapy (RLT) utilizes a radioactive atom coupled with a targeting molecule. The underlying principle is to deliver a highly potent dose of radiation directly to cancer cells while sparing healthy tissues as much as possible.

The promising prospects of alpha emitters :

Two types of radionuclides can be used in RLT: alpha particles and beta particles emitters. Beta RLT has a longer history of clinical use since it was chemically easier to develop and beta emitters were more easily available. The two RLTs that are already commercialized (Lutathera and Pluvicto by Novartis) use Lutetium-177, which emits beta particles.

However, alpha particles present 2 key advantages for applications in RLTs :

1. Greater Biological Effectiveness:

Alpha particles have a higher linear energy transfer than beta particles. This provokes irreparable DNA double strand breaks to cells in the immediate surroundings of the emission. As a consequence, contrary to beta emitters, this specific mechanism of action hinders the development of processes of resistance or immune escape in tumor cells. 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. Another advantage of alpha emissions is that it does not require internalization of vectors to be effective,

contrary to beta emitters that are not potent enough.

2. Limited toxicity via Short Range:

Alpha particles have very short emission range compared to beta particles. They deposit a large amount of radiation within a short distance, typically a few cell diameters. It results to an increased cytotoxic potential toward cancer cells while limiting toxicity to nearby healthy cells. Thanks to their short range, alpha particles are well-suited for treating micrometastases that may not be easily targeted with other therapies.

Orano Med can meet the challenges of RLT production

Overall, radioligand therapy represents an exciting and evolving field in cancer treatment, with an expected growth of +30% per year over the next ten years (Medraysintell 2021). Nevertheless, the production of RLTs faces several challenges that currently limit their availability and adoption in clinical practice. Radionuclides used in RLT require specialized nuclear production facilities. It is also partly for this reason that no targeted alphatherapy has yet been commercialized. Today, no single company masters the entire value chain, from the development of these new therapies to their production at industrial scale for worldwide distribution.

Orano Med's ambition

That is why Orano Med has a double ambition :

- Develop a robust pipeline of RLTs using lead-212, an alpha emitter, and thus bring to the market the world's first targeted alphatherapies to offer new breakthrough solutions for patients with high unmet medical needs in the oncology field;
- Provide a robust manufacturing and supply chain for these innovative drugs by developing a unique industrial platform and demonstrating its capacity to guarantee a reliable global commercial supply of lead-212 based treatments.

Attached Files:

- Presentation_Orano_Med.pdf

History of the development of the solution/product

Orano Med's origins

In the 2000s, the Areva group (now Orano) looked at the opportunities for recycling materials from its nuclear energy activities. Among them nuclear medicine and targeted cancer alphatherapy appeared to be very promising. Lead-212 was identified as offering solid scientific basis and real applications, and Orano's know-how enabled it to meet the challenges of its supply. Conclusive preclinical studies conducted in collaboration with the National Cancer Institute (NCI) in the United States led to the creation of Orano Med in 2009. In 2012, Orano Med launched the first clinical trial of targeted alphatherapy with lead-212 which confirmed the potential of these therapies.

AlphaMedix development

In 2018, in partnership with RadioMedix (a US biotech based in Houston, Texas), Orano Med initiated a phase I clinical trial to evaluate the safety and efficacy of AlphaMedix. AlphaMedix is a somatostatin receptor targeting peptide radiolabeled with lead-212 that could be used in the treatment of neuroendocrine tumors. Despite the success of Lutathera (a beta RLT targeting the same receptor)

that is today considered the standard of care for gastroenteropancreatic neuroendocrine tumors, there remains significant unmet medical needs and clear room for improvements, both in terms of safety and efficacy.

- Phase I results not only showed that AlphaMedix treatment was well tolerated, but an objective response rate (ORR) of 80% was observed for subjects treated at the recommended phase 2 dose. Moreover, an additional cohort of subjects who progressed after receiving a beta RLT with Lu-177 or Y-90 was enrolled. Presented during ASCO 2022, an ORR of 50% was demonstrated in these subjects.
- Ongoing phase II: Based on these very promising results, a phase II trial was launched in 2021. In May 2023, the enrolment for this trial has been completed and remarkably, the ORR endpoint has already been achieved and is more than twice as high as the current standard of care, representing a best-in-class potential for AlphaMedix
- Orano Med and RadioMedix plan to apply for a "Breakthrough designation" from the FDA for AlphaMedix in 2023 and to launch the phase III in 2024.

A solid portfolio of targeted alphatherapies with lead-212 in development

In parallel, based on the unique properties of lead-212, state-of-the-art manufacturing capabilities and strong translational expertise, Orano Med is developing a multi asset portfolio to combine lead-212 with diverse biological vectors targeting different cancer receptors. Our pipeline is composed of a mix of partnered assets and internal developments.

- In 2022, Orano Med initiated a phase I clinical trial to evaluate the safety and efficacy of ²¹²Pb-GRPR in patients with advanced solid tumors that express gastrin-releasing peptide receptor (GRPR). It is the first targeted alpha therapy targeting GRPR, a protein highly expressed in prostate cancer, lung cancer, breast cancer and other solid tumors.
- Since 2012, Orano Med has established a long-standing partnership with Roche, a well known recognized leader in oncology, to create a novel, advanced alpha radioimmunotherapy platform based on pretargeted approach. The two companies share a preclinical laboratory in France dedicated to the development of this promising technology.
- Orano Med has several other assets under preclinical development with very promising results, such as our partnership with Bicycle Therapeutics on the development of targeted alphatheray targeting MT1, or with Nordic Nanovector for the treatment of chronic lymphocytic leukemia.

Orano Med is developing a unique industrial platform

On the industrial side, development of targeted alphatherapies has long been hindered by a lack of supply of alpha emitting isotopes meeting three important criteria: purity meeting radiopharmaceutical standards, reliable production capacity sufficient to meet global needs, and economic competitiveness.

Since 2013 and the construction of the Maurice Tubiana Laboratory in France, Orano Med has developed and industrialized a patented, 100% chemical process allowing production of Pb-212 on a

large scale and at a reasonable cost. Moreover, with a unique and proprietary source of raw material (Thorium-232), we are autonomous for the production of our drugs, with practically unlimited supply of lead-212.

Orano Med is now preparing the future commercialization of lead-212 conjugated drugs and the construction of industrial facilities throughout the world. In the US at Brownsburg, Indiana, the first Alpha Therapy Laboratory (ATLab, GMP plant for Phase III & commercial supply) is currently under construction. In 2024, it will commence the large-scale production of targeted alphatherapy treatments and their distribution in North America. Another ATLabs is under construction in France for EU supply. The construction of other ATLabs will be launched shortly to cover global needs.

Attached Files:

- OranoMed_AlphaMedix_development.pdf

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

Orano Med is leveraging the ideal properties of lead-212

Despite the initial successes of beta RLTs based on Lutetium-177 and the promising advantages of alpha emitters, no alpha RLT has been commercialized so far. 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. Lead-212 presents the ideal radioactive and chemical properties for application in radioligand therapies:

- With only one single alpha decay, toxicity to healthy organs is limited;
- Another isotope of lead, lead-203, is a gamma emitter, opening up possibilities for the development of theranostic approaches;
- Its relatively short half-life (10.6 hours) makes nuclear waste management not very constraining and outpatient administration possible, and thus makes targeted alphatherapies with lead-212 innovative treatments with limited impact on the healthcare system and hospitals in particular.

Orano Med is developing a unique technological platform on targeted alphatherapy with lead-212. Orano Med has thus developed a strong expertise and a unique technological platform enabling it to couple this isotope to a very large number of vectors, and then to optimize the biological properties of the drug (pharmacokinetics, toxicity, tumor targeting, etc). Its preclinical laboratory dedicated to the development of lead-212 targeted alpha therapy treatments in Plano, Texas, is fully equipped to conduct the necessary in vitro and in vivo preclinical studies as well as to perform activities of peptide synthesis, bioconjugation, radiolabeling and analytical testing. We have also demonstrated a strong track record at combining our Science and with Clinical teams to ensure translation to the clinic of these potential best-in-class medicines. Thanks to this expertise, Orano Med can potentially combine lead-212 with a large number of biological vectors for an almost illimited range of applications in oncology.

Orano Med is the only company capable of both developing and producing at a commercial scale targeted alphatherapies

Because reliability of supply of alpha emitters has long hindered the development of targeted alphatherapy, Orano Med has developed a unique proprietary process and platform and is massively

investing in its industrial capabilities to master the entire value chain from drug development to production and distribution of these breakthrough treatments. While competing players are positioned either in drugs development or in nuclear radionuclide production, Orano Med's unique position aims to revolution the field of RLTs.

Attached Files:

- [OranoMed_pipeline_development.pdf](#)

Please provide appropriate references (ie Pubmed links)

Results of the first clinical trial on targeted alphatherapy with lead-212 :

<https://pubmed.ncbi.nlm.nih.gov/27906723/>

AlphaMedix phase I results :

<https://pubmed.ncbi.nlm.nih.gov/34992153/>

AlphaMedix clinical results presented at ASCO 2022 :

<https://www.oranomed.com/en/resources/news/2022/orano-med-presented-a-poster-at-2022-asco-annual-meeting>

Preclinical results of AlphaMedix:

<https://pubmed.ncbi.nlm.nih.gov/30926632/>

Preclinical results of the collaboration with Bicycle Therapeutics presented at TIDES 2023:

<https://www.oranomed.com/en/orano-med-ressources/publications/publications/potent-anti-tumor-activity-of-a-lead-212-labelled-mt1-mmp-targeting-bicycle-radionuclide-conjugate>

Preclinical results of the collaboration with Nordic Nanovector

<https://pubmed.ncbi.nlm.nih.gov/32187209/>

Preclinical results of the collaboration with Toulouse University Hospitals (France)

<https://pubmed.ncbi.nlm.nih.gov/31862796/>