ALL THINGS NUCLEAR – PORTLAND LIFE UNIFYING SCIENCES NEWSLETTER

FEBRUARY 2025

Over the past year, large pharmaceutical companies have invested billions in targeted radionuclide therapy (TRT), an emerging class of targeted cancer treatments that have been referred to as "the fourth pillar of cancer care." Several high-profile Mergers and Acquisitions (M&A) deals in late 2023 and the first half of 2024 reflected this surge of interest, which propagated into the second half of 2024, albeit somewhat reduced in scope.

In particular, Orano Med LLC (Orano Med) and its partner have entered into an exclusive licensing agreement with Sanofi S.A. (Sanofi) for AlphaMedix™, a late-stage asset currently under evaluation for treating adult patients with a specific type of neuroendocrine tumor (NET). This agreement follows the U.S. Food and Drug Administration's (FDA) decision earlier in 2024 to grant AlphaMedix breakthrough therapy designation, recognizing its potential to deliver substantial tumour reduction and a favourable safety profile. Under the terms of the agreement, Orano Med and its partner will receive an upfront payment of €100 million, up to €220 million in sales milestone payments and tiered royalties. In addition to reaffirming interest from yet another major pharmaceutical company, we see this development as an important milestone for the recognition of the ever-expanding arsenal of radioisotopes available to industry and clinicians in battling cancer. We think AlphaMedix is well positioned to be a pioneering and leading radiotherapeutic leveraging the use of the potent alpha-emitting radioisotope 212Pb (lead), with multiple other players working towards the expansion of both the supply chain for 212Pb as well as a suite of 212Pb based therapies for multiple cancer indications.

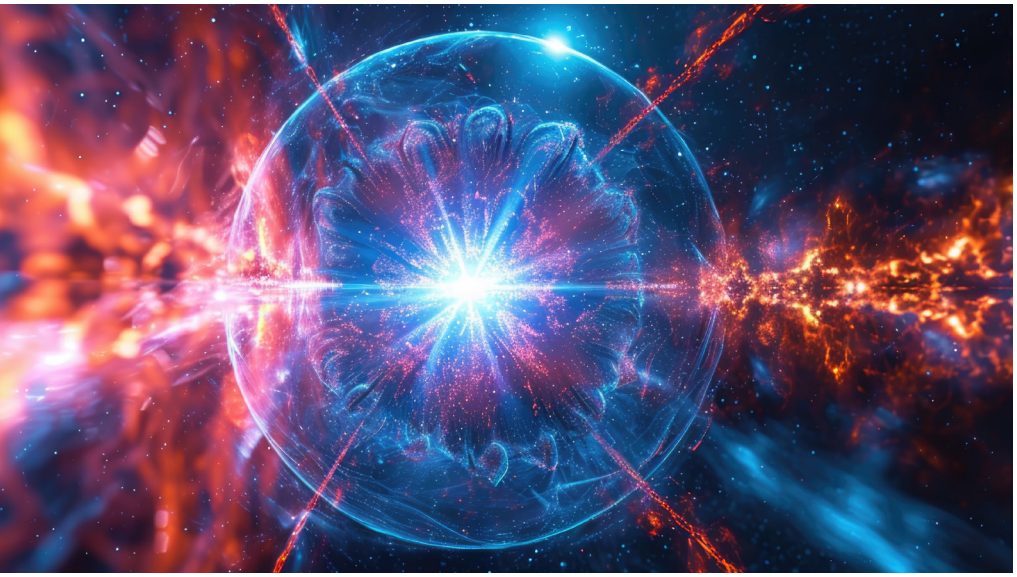
The industry momentum is also evident in a proliferation of TRT assets seeking to treat late stage prostate cancer, where Prostate Specific Membrane Antigen (PSMA) remains a highly pursued target, with over 15 programs in development as of 2024. Among a growing number of contenders, Telix Pharmaceuticals Limited (Telix), Lantheus Holdings, Inc. (Lantheus), Point Biopharma Global Inc. (Point Biopharma), a part of Eli Lilly and Company (Eli Lilly) and Curium Pharma are progressing their late-stage clinical programs in metastatic prostate cancer, with ambitions to challenge Novartis AG's (Novartis) PLUVICTO™, the first-in-class therapeutic, which received US market approval in 2022 and has also recently been approved for public reimbursement in Canada. With approximately US$1.4 billion in revenue generated in 2024, PLUVICTO is projected to reach peak sales of over US$5 billion, highlighting the potential in the field. Somewhat bucking the trend, Clarity Pharmaceuticals Ltd (Clarity Pharmaceuticals), also one of our investee companies, has chosen to develop a theranostic pair using 64Cu/67Cu (copper) to treat patients expressing the Gastrin-Releasing Peptide Receptor (GRPR), in addition to its own PSMA program.

There is also much excitement surrounding the development of

radiopharmaceuticals to diagnose and treat cancers beyond prostate and neuroendocrine tumors. Telix has achieved significant milestones by submitting regulatory applications to the U.S. Food and Drug Administration (FDA) for its innovative radio-diagnostic agents, Zircaix® and Pixclara®. Zircaix aims to improve the diagnosis of specific types of renal tumors, while Pixclara has the potential to precisely image certain types of brain cancers. Contingent upon FDA approval, these agents could be among the first newer generation radiopharmaceuticals to extend beyond prostate and neuroendocrine cancers, reinforcing the versatility of this modality.

A variety of other cancer-associated targets are also being explored, from Melanocortin 1 receptor (MC1R) in melanoma to Fibroblast Activating Protein (FAP) with potential application across tumours. These initiatives are being spearheaded by a diverse group of players, from large pharmaceuticals like Novartis and AstraZeneca plc (AstraZeneca) to specialized radiopharma companies such as Perspective Therapeutics, Inc. (Perspective Therapeutics) and Clarity Pharmaceuticals. While varying degrees of safety and efficacy have been demonstrated, we note that many of these assets are in earlier stages of development, with in-human data from small patient cohorts. We believe there remains plenty of room for the assets to mature as the field is still nascent, with ample growth potential. Equally, the ever expanding field of radioisotopes, combined with a viable commercial pathway, the potential adjustments in dosimetry, and the potential combination with other cancer targeting modalities such as immunotherapy present numerous potential avenues of growth.

On the private radiopharma companies' front, ITM Isotope Technologies Munich SE (ITM), another frontrunner, has also made strides. The company announced positive topline results from its Phase 3 COMPETE trial, which tested ITM-11, (n.c.a.[no-carrier-added] 177Lu-edotreotide) a targeted radiopharmaceutical therapy, in patients with Grade 1 or Grade 2 gastroenteropancreatic neuroendocrine tumors (GEP-NETs). ITM-11 met the primary endpoint of improving progression-free survival (PFS) compared to the standard treatment, everolimus. The therapy was well-tolerated, with favorable safety results. The trial enrolled 309 patients and showed that ITM-11 demonstrated a significant benefit over everolimus in this patient group. At the same time, the company continues to advance its broad pipeline of diagnostic and therapeutic agents. In the second half of 2024, ITM further expanded its pipeline with the strategic acquisition of diagnostic and therapeutic agents from Debiopharm International SA (Debiopharm), with potential applicability in a diverse range of tumours including renal and pancreatic cancers.



Looking beyond radiopharmaceuticals, several notable developments are shaping the broader oncology landscape. The recent approvals of Imfinzi®, marketed by AstraZeneca, and Imdelltra®, marketed by Amgen Inc., have provided new treatment options for patients with small cell lung cancer, a particularly challenging and hard-to-treat cancer. These approvals highlight the growing strength of immunotherapy in tackling complex cancers. At the same time, targeted therapies are gaining increasing attention, especially those designed to address specific mutations in high-incidence cancers. In breast cancer, for example, a variety of therapies — ranging from those that block estrogen signaling to those targeting specific mutations — are advancing through late-stage clinical trials, with data expected shortly. In light of patent expirations, some of these innovations have similarly garnered interest from large pharmaceutical companies, who are positioning themselves to catch the next wave of targeted cancer treatments.

Indeed, we believe 2025 is destined to be another year of robust advancements in precision oncology, with continued advancements in therapeutic modalities such as Antibody Drug Conjugates (ADCs), Immunotherapies, targeted therapies, including TRTs. These developments are laying the groundwork for precision medicine, continuing to facilitate the transition from a one-size-fits-all approach toward a more personalized treatment approach, tailored to the unique characteristics of each patient's cancer.

With that being said, the overall biotech sector is exercising cautious optimism as U.S. President Donald Trump takes on his second term. The Trump administration's focus on deregulation and potential tax reforms could create a more favorable business environment. However, uncertainties surrounding healthcare policies, including the nomination of Robert F. Kennedy Junior as U.S. Secretary of Health and Human Services, and the current administration's stance on international cooperation, have led to a largely cautious sentiment in the broader healthcare and biotech landscape.

Despite these potential changes, we remain of the view that central to the biotech sector's progress are fundamental scientific advancements, which have and will continue to drive innovation. We believe that the potential to improve healthcare outcomes for patients in need stands firmly as the foundation of the sector's long-term promise, despite ever-changing external factors.

RECENT INDUSTRY DEVELOPMENTS

Aktis Oncology announced an oversubscribed and upsized US$175million Series B financing led by RA Capital Management, L.P. and co-led by RTW Investments, LP and Janus Henderson Investors. The company is focused on the development of AKY-1189, its first-in-class miniprotein alpha radioconjugate targeting Nectin-4 in development for several tumor types.

Alpha-9 Oncology, Inc. raised a US$175 million series C round to bankroll its clinical-stage radiopharmaceutical drugs, although the exact details of the biotech's pipeline remain hazy. The Canadian company did announce in May that it had dosed the first patient in a phase 1 study of a radiodiagnostic targeting melanocortin 1 receptor (MC1R).

Curium Pharma announced that its ECLIPSE trial met its primary endpoint. ECLIPSE is a pivotal Phase 3, multi-center, open-label, randomized clinical trial comparing the safety and efficacy of 177Lu-PSMA-I&T (INN: lutetium (177Lu) zadavotide guraxetan) versus hormone therapy in patients with metastatic castration-resistant prostate cancer. The ECLIPSE trial demonstrated a statistically significant and clinically meaningful improvement in the median radiographic progression-free survival (rPFS) of patients with prostate-specific membrane antigen (PSMA) positive metastatic castration-resistant prostate cancer (mCRPC) after treatment with up to 6 doses of 200 measured in millicuries (mCi) (7.4 gigabecquerels (GBq) of 177Lu-PSMA-I&T in patients previously treated with an androgen receptor pathway inhibitor (ARPI) compared to a change in ARPI.

Clarity Pharmaceuticals announced the development of a novel radiopharmaceutical called Specific Activity Radiopharmaceutical - bisFibroblast Activation Protein (SAR-bisFAP), which was designed for both the diagnosis and treatment of various cancers and leverages copper (Cu)isotopes, with Cu-64 used for imaging and Cu-67 used for therapy.

Clarity Pharmaceuticals entered into a supply agreement with TerraPower for Ac-225 for Clarity's 225Ac-bisPSMA (bisProstate-Specific Membrane Antigen) program effective July 2024. Supply under this agreement was expected to commence in November 2024. The supply agreement is for an initial period of 2 years and can be extended under the terms of the contract.

ITM gained exclusive global development and commercialization rights to **Debiopharm's** peptide-based theranostic pair - Debio 0228 ([177Lu]Lu-DPI-4452) and Debio 0328 ([68Ga]Ga-DPI-4452) - to target Carbonic Anhydrase IX (CAIX). Debiopharm is to receive upfront, development and regulatory milestone payments of ~€300M, as well as potential commercial milestones.

ITM appointed Dr. Andrew Cavey as the new Chief Executive Officer (CEO) of ITM replacing Steffen Schuster who stepped into the company's Supervisory Board. Dr. Cavey's previous experience in his role as Senior Vice President, Head of Global Program Leaders, Hematology, Oncology, Cell Therapy at Bristol Myers Squibb Company brings vast experience in global markets, strategy, clinical development and commercialization and, we believe, is well suited to lead the company into the next stage of growth.

Lantheus announced acquisition of Meilleur Technologies and has Weigt Watchers International, Inc. exclusive rights to ß amyloid PET imaging agent, Neuroimaging Agent for Visualization (NAV)-4694, (F18-flutafuranol), which is currently in Phase 3 for Alzheimer's disease. The acquisition complements Lantheus' other Alzheimer's Disease (AD) PET imaging agent MK-6240, which targets tau tangles. No specific financial terms were disclosed. The Press Release stated that Lantheus will provide an upfront payment as well as potential additional development and commercial milestone payments.

Lilly signed a strategic agreement with **Radionetics Oncology**, a spinout of Crinetics (CRNX), in July, with an upfront payment of US$140 million and the exclusive right to acquire the company upon conclusion of an exercise period for $1 billion. Lilly gained access to Radionetics' proprietary **G Protein-Coupled Receptor (GPCR)** targeting small molecule radiopharmaceuticals and its discovery platform for the treatment of a broad range of solid tumors. This is Lilly's second radiopharmaceutical collaboration this year – the first one was announced in May with Aktis Oncology for $60 million upfront and eligibility for milestone payments of up to $1.1 billion. Lilly also acquired POINT for ~$1.4 billion in October 2023.

Lilly continues with its investments into radiopharmaceuticals, with a reported US$10 million convertible note in **Ionetix's** financing led by Tees River. Other existing investors also backed the company with $10 million. Ionetix is an isotope manufacturer based in Lansing, Michigan and has a deep relationship with POINT, which Lilly acquired last year. In Nov 2021, POINT announced an Ac-225 supply agreement with Ionetix and in May 2023 POINT invested $10mm into Ionetix Alpha Corp. With this financing, Ionetix will fund the development of its core technology and expansion of the current cyclotron network. The company estimates that by the end of next year it will be able to provide ~26,000 patient doses a year.

Novartis invested US$200 million into its radioligand therapy manufacturing capabilities with a new site in California and the expansion of an existing site in Indianapolis. The Indianapolis site will produce radioisotopes for the drugmaker's products Pluvicto and Lutathera. The new location in Carlsbad, CA, will be Novartis' third radioligand therapy manufacturing site in the US and is part of an effort to "create resiliency in its manufacturing network and optimize the delivery of medicines to patients on the West Coast," according to the company.

Novartis Pharmaceuticals Canada announced the successful conclusion of negotiations with the pan-Canadian Pharmaceutical Alliance for the public reimbursement of Pluvicto for the treatment of adult patients with prostate-specific membrane antigen (PSMA) positive metastatic castration-resistant prostate cancer (mCRPC) who have received at least one androgen receptor pathway inhibitor (APRI) and at least one taxane-based chemotherapy.

Perspective Therapeutics announced that the U.S. Food and Drug Administration (the "FDA") granted Fast Track Designation for the development of 212Pb VMT01 for the diagnosis and treatment of patients with unresectable or metastatic melanoma and who have demonstrated MC1R tumor expression. Melanocortin 1 receptor, or "MC1R," is a protein that can be overexpressed in metastatic melanoma. The FDA's Fast Track Designation is one of several approaches utilized by the FDA to expedite development and review of potential medicines for serious conditions and that fulfill unmet medical needs. Programs that receive Fast Track Designation are entitled to more frequent interactions with the FDA on the development of a drug development plan, as well as eligibility for accelerated approval, priority review and rolling review.

Sanofi announced a licensing deal worth a total of €100 million in upfront payments with €220 million in potential sales milestones for global rights to AlphaMedix, a 212Pb-DOTAMTATE neuroendocrine tumor treatment that is completing Phase 2 development from **Orano Med and its partner.** Sanofi will be responsible for global commercialization, while Orano Med will be responsible for manufacturing.

Sanofi is continuing to invest in radiopharmaceuticals, paying €300 million for a 16% stake in Orano Med, which is valuing Orano Med at about €1.9billion. Sanofi highlighted Orano Med's "vast stock of raw materials and patented manufacturing process" to ensure reliable supply of lead based therapies. Orano Med has an alpha therapy production site near Indianapolis and started construction last year on a facility in France for the European market. The Orano Group subsidiary has a research unit in Plano, Texas. Orano Med's pipeline includes wholly owned Phase 1 and preclinical solid tumors and prostate cancer programs. It also has partnerships with Roche and Molecular Partners.

Telix announced that FDA accepted its New Drug Application (NDA) for TLX007-CDx for new PSMA-PET imaging agent for prostate cancer, with a Prescription Drug User Fee Act (PDUFA) goal date of March 24, 2025. Telix also submitted a Biologics License Application to the U.S. FDA for TLX250-CDx, its investigational PET drug product used for the non-invasive diagnosis of kidney cancer. The company issued an A$650 million 2.375% convertible note due 2029. The net proceeds are intended to accelerate key clinical development programs across the company's theranostic portfolio, including label-expansion studies for its diagnostic imaging agents and funding the pivotal trials for kidney and brain cancer therapy programs. In addition, the funding will provide financial flexibility for Telix to explore significant M&A transactions and continued investment in the global supply chain and manufacturing capabilities.

Telix completed the installation of two new cyclotrons at Telix Manufacturing Solutions (TMS) in Brussels South, Belgium. This will allow for the production of radioisotopes and patient doses on-site beginning in 2025.

Telix received the FDA nod for its New Drug Application and granted priority review for TLX101-CDx (Pixclara®) Brain Cancer Imaging Agent.

Telix has announced the spin-off of Rhine Pharma GmbH (Rhine Pharma), a company focused on improving global access to radiopharmaceuticals for cancer imaging and treatment. Rhine Pharma emerged from a collaboration with Heidelberg University Hospital, developing the next generation theranostic compound RHN001, which is advancing into clinical trials for prostate cancer. The spin-off allows Telix to focus on new opportunities while enabling Rhine Pharma to pursue its mission more effectively.

U.S. Centers for Medicare & Medicaid Services (CMS) issued the CY2025 (Calendar Year 2025) Proposed Medicare Hospital Outpatient Prospective Payment System (OPPS) Rule including improved payment for diagnostic radiopharmaceuticals, which was received with great interest by the industry and the investment public, principally as it impacted the trading price of Lantheus and Telix' stock. Medicare aims to separately reimburse the cost of specialized diagnostic radiopharmaceuticals that exceed US$630 per day. Following the expiry of the pass-through payments, radiodiagnostics such as Lantheus' Pylarify and Telix's Illucix, will continue to be paid separately by CMS for traditional Medicare Fee for Service patients in the hospital outpatient setting instead of costs being incorporated into the payment rates for nuclear medicine tests.

***About PLUS:*

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Glossary:

Bioconjugation means a chemical process of linking biological molecules with other molecules.

Cyclotron facility means a facility with particle accelerators.

Fibroblast Activation Protein-Alpha (FAP) means a protein highly expressed in some types of cancer cells.

Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) means slow-growing neoplasms that arise from the neuroendocrine system of the gastrointestinal tract and pancreas. Gastrointestinal tract is mostly the stomach and intestines.

Isotope means each of two or more forms of the same element that contain equal numbers of protons but different numbers of neutrons in their nuclei, and hence differ in relative atomic mass but not in chemical properties; in particular, a radioactive form of an element.

Metastasis means the spread of cancer cells from the place where they first formed to another part of the body. In metastasis, cancer cells break away from the original (primary) tumour, travel through the blood or lymph system, and form a new tumour in other organs or tissues of the body. The new, metastatic tumour is the same type of cancer as the primary tumour. The plural form of metastasis is metastases.

Neuroendocrine tumour (NET) means a tumour that forms from cells that release hormones into the blood in response to a signal from the nervous system.

Non-Carrier Added (NCA) means a pure radioisotope without contamination from stable isotopes.

Peptide Receptor Radionuclide Therapy (PRRT) means therapy delivering radiation via peptides that bind to specific receptors on tumors.

Positron Emission Tomography (PET) means imaging technique using radioactive tracers to visualize certain activities in the body.

Precision oncology means molecular profiling of tumors to identify targetable alterations, is rapidly developing and has entered the mainstream of clinical practice.

Prostate-specific membrane antigen (PSMA) means a membrane protein which contributes to prostate cancer's development and is seen in a higher amounts in prostate cancer cells.

Radioconjugates means Molecules which generally combine a radioactive isotope with a targeting agent.

Radioligand therapy means a targeted form of cancer treatment that delivers radiation directly to cancer cells.

Radionuclide therapy means a type of treatment using targeted radioactive elements to destroy cancer cells.

Radioisotopes means radioactive versions of elements.

Radiopharmaceutical means a radioactive drug composed of a radionuclide and a pharmaceutical that is used for diagnosis or therapy.

Somatostatin means a peptide hormone that prevents the release of growth hormone from the pituitary gland.

Somatostatin receptors (SSTRs) means receptors that are expressed in high levels in gastroenteropancreatic neuroendocrine tumors.

Standard of Care (SoC) medical treatment guideline.

Targeted Alpha Radioligand Therapies (ART) means a type of PRRT which utilizes alpha-particle-emitting radioisotopes – same as Targeted Alpha-Emitter Therapy (TAT).

Targeted Alpha-Emitter Therapy means a type of PRRT which utilizes alpha-particle-emitting radioisotopes.

Targeted radionuclide therapy (TRT) means a form of treatment that delivers therapeutic doses of radiation to malignant tumours, for example, by administration of a radiolabeled molecule designed to seek out certain cells.

Theranostics means a new field of medicine which combines specific targeted therapy based on specific targeted diagnostic tests.

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PIC25-009-E (02/25)