Horizon Scanning Report: Horizon scan and landscape analysis of innovations in therapeutic radioligand technologies

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List of abbreviations

In-111	Indium-111
I-131	Iodine-131
Lu-177	Lutetium-177
Ra-223	Radium-223
P-32	Phosphorus-32
Y-90	Yttrium-90
ICTRP	International Clinical Trials Registry Platform
IO	Innovation Observatory
MHRA	Medicines and Healthcare products Regulatory Agency
MRT	Molecular Radiotherapy
NaI	Sodium iodide
NET	Neuroendocrine tumour
URL	Uniform Resource Locator

Glossary

Nuclear medicine: is a specialised field of medicine covering all aspects of the use of radioactive substances that are either injected in or ingested by humans with the aim to diagnose or treat a disease.

Radionuclide: is a substance that degrades in a very constant manner over time and emits one or several radiations. This degradation or decay is defined by a constant, the period (or half-life) corresponding to the time it takes for half of the remaining substance to disappear. This half-life is specific for each radionuclide.

Radiopharmaceutical: is a radioactive compound used for diagnosis and therapeutic treatment of human diseases. A radiopharmaceutical consists of two components: a radionuclide and a pharmaceutical.

Radioligand therapy/molecular radiotherapy: is a highly targeted cancer therapy. A radioligand is made of two parts: a ligand, which is able to find cancer cells that present a particular receptor, and a radioisotope, which is able to treat the cancer.

Introduction

Molecular radiotherapy (MRT), also known as radionuclide/radioligand therapy, is a branch of nuclear medicine referring to the delivery of radiation to tissue via the interaction of a radiopharmaceutical with molecular sites or receptors, however the term can generally encompass all treatments with radiotherapeutics.[1,2] This form of therapy uses a biologic or other vehicle labelled with a radionuclide to deliver a cytotoxic level of radiation to disease sites.[3,4] MRT represents a dynamically evolving field, particularly in terms of quantifying uptake in both normal and malignant tissues, with a notable 250% increase in utilisation observed in the UK from 2007 to 2017.[5,6]

In the UK, the predominant form of MRT, or therapeutic radioligand technologies, is the use of I-131 NaI (sodium iodide), primarily employed for treating benign thyroid diseases and thyroid cancer, with its initial application dating back to 1941 in the United States.[1,6] Therapeutic radioligand technologies also hold a well-established role in managing bone metastases and associated bone pain, with key radiopharmaceuticals including beta-emitting strontium-89 (Sr-89) dichloride (Metastron), samarium-153 (Sm-153) lexidronam (Quadramet), and alpha-emitting radium-223 (Ra-223) dichloride (Xofigo).[6] Furthermore, radiolabelled peptides have emerged as a preferred treatment modality for neuroendocrine tumours (NETs), with indium-111 (In-111) octreotide and yttrium-90 (Y-90) DOTATATE historically used, and the inclusion of lutetium-177 (Lu-177) DOTATATE as a standard therapy following its licensing.[1]

To utilise therapeutic radioligand technologies for clinical use, requires the production of radionuclides. Desired radionuclides are sometimes created in a generator where a parent isotope decays to the required daughter radionuclide. These can have varied half-lives. For radionuclides to be used effectively within their half-life period, it is essential to create, isolate, perform synthesis with the targeting molecule, while also safeguarding against unwanted consequences like long-lived and/or toxic daughters. Radionuclides with a shorter half-life must be isolated closer to the time and site of treatment, whereas those with longer half-life can be produced in a specialised, central location and subsequently delivered to hospitals, while ensuring that the daughters can remain stable during delivery. Radionuclides with longer half-lives are often complexed with long-lived antibodies, the long circulation time of which can potentially increase the risk of non-specific toxicity and off-target effects.[7]

The global concern regarding medical radionuclide shortages arises from constraints on source materials and the complexities inherent in production processes. While numerous radionuclides occur naturally, obtaining substantial quantities of purified material necessitates sophisticated infrastructure, such as accelerators or nuclear reactors, along with the requisite facilities and expertise for chemically isolating the desired radionuclide from the array of others generated during production. Alternative approaches include generator systems, wherein a parent radionuclide undergoes decay to yield the desired radionuclide, subsequently extracted for medical use, as well as cyclotron technology, which accelerates and directs a range of particles—such as protons, alpha particles, lithium, and carbon ions—onto a target material to produce the required radionuclides.[7]

This report uses the term therapeutic radioligand technologies from this point forward, but there are various terms used for the approach, including molecular radiotherapy, peptide-receptor radionuclide therapy (PRRT), systemic radiation therapy, targeted radionuclide therapy and targeted radiotherapy.

Regulation of Therapeutic Radioligand Technologies

It is important to note that the regulatory framework, which governs the approval of therapeutic radioligand technologies, varies between countries. In some countries, radioligands are classified and regulated as pharmaceuticals, but in others, they are classified as radioactive substances. Regulatory frameworks developed for conventional medicines may need to be revised both internationally and nationally to ensure appropriate evaluation of radioligand therapy and radionuclides.

In the UK, the MHRA is responsible for new therapies and products for clinical use.[8] The MHRA considers therapeutic radioligand technologies as medicinal products and treats it as such in the approval process. This process requires that evidence is provided regarding safety and efficacy of the medicinal product to the MHRA for approval. However, it has been highlighted that the current regulatory process was not designed to take into consideration highly targeted and personalised medicines, which includes therapeutic radioligand technologies. To date, a limited number of therapeutic radioligand technologies, Lu-177 oxodetreotide, Y-90 ibritumomab tiuxetan, and Ra-223 dichloride, have been licensed in the UK for neuroendocrine tumours (NETs), lymphoma, and metastatic castration resistant prostate cancer respectively.[8,9]

The need for further research has been recognised. In 2016, the National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group published a report 'Identifying opportunities to promote progress in molecular radiotherapy research in the UK'.[1] Therefore, identifying therapeutic radioligand technologies early in the development process is imperative to make informed decisions and to prepare for the future development of these innovations. The identification of these therapeutic radioligands may also contribute to significant advancements in medical treatments. By targeting specific receptors in the body, therapeutic radioligands have the potential to deliver precise and effective therapies, minimising damage to surrounding healthy tissues. This could lead to improved outcomes, reduced side effects, and enhanced quality of life for patients undergoing treatment. In recognition of this background and to best inform future developments in service provision, the All Wales Molecular Radiotherapy (MRT) Strategic Programme requested that the NIHR Innovation Observatory (IO) conduct horizon scanning activities to identify therapeutic radioligands that meet stakeholder requirements (please refer to table 1 for technologies in scope).

Methods

Horizon Scanning for Therapeutic Radioligand Technologies

The horizon scanning methods developed by the IO for the identification and assessment of the pipeline of innovative therapeutic radioligand technologies currently in clinical trials, consisted of firstly, the identification and selection of relevant information sources that detected 'signals' of emerging therapeutic radioligand technologies and secondly, the selection and analysis of those signals against the scope of this project. This horizon scan report provides a comprehensive overview of upcoming therapeutic radioligand technologies and future indications in the pipeline. Table 1 details the inclusion criteria for this scan.

Table 1. Therapeutic radioligand technologies in scope

Criteria	
Technology name	All therapeutic radioligand technologies
Technology use or application	Patients receiving radioligand technologies for therapeutic or theranostic purposes
Technology stage of development	Phase 2/3 Phase 3 Phase 4
Date of registration	2020 onwards
Trial status	Ongoing (Recruiting, not yet recruiting, active, completed, enrolling by invitation, unknown)

Search Strategy and Sources

For the identification of signals of development on therapeutic radioligand technologies, the following sources of information were used:

- Clinicaltrials.gov trial registry, used to identify clinical trials in development largely in the US but also in global trial locations.
- International Clinical Trials Registry Platform (ICTRP) by the World Health Organisation (WHO), containing trial information from 17 national trial registries across the globe, was used to identify European/global trials.

The specific registries were selected based on their comprehensive coverage of clinical trials in different regions, ensuring a global representation of ongoing research. Additionally, the registries were chosen for their reliability and credibility in providing accurate and up-to-date information on clinical trials.

The search strategy was designed to maximise sensitivity but also to increase precision. It consisted of a combination of key words such as 'radionuclide', 'therapeutic radiopharmaceutical', 'theranostic' or 'theragnostic', and specific radionuclides of interest that were agreed at protocol stage with stakeholders. These included: 'phosphorus-32', 'yttrium-90', 'iodine-131', 'holmium-166', 'lutetium-177', 'radium-223', 'actinium-225' and 'thorium-227'. A detailed description of the search strategy for clinical trials is provided in Appendix 1.

Data extraction

A data extraction form was created in Excel to systematically collect information about each of the technologies identified the met the inclusion criteria outlines in Table 1 above. We systematically collected the following data for each technology:

- General information: trial title and trial status (as agreed on project proposal)
- Product information: name of intervention, name of radionuclide, and name of ligand
- Patient group: indication, therapeutic area according to NICE categories, cancer or non-cancer, gender and age of participants
- Trial information: trial ID, phase, availability of trial results, outcome measures, number of enrolled participants, further study design information, date of trial registration date of start and end of trial, sponsor, funder type, location of trial recruitment and URL.
- Regulatory information of technology in trial, later enriched with information gathered from the MHRA and NICE websites.

We piloted the data extraction form with the few technologies that met the inclusion criteria, and we invited our stakeholders to provide feedback. This was done to ensure that the data extraction form would accurately capture the different aspects of the technologies needed for their analysis in line with stakeholder's needs and to give stakeholders the opportunity to review and provide feedback. No changes needed to be made to the data extraction form and it was approved in January 2024.

Results

Our horizon scanning searches identified a total of 80 clinical trials that met the search criteria. After applying the agreed time limits (2020 – current) phase of development (phase 2/3, 3, and 4) and trial status (in progress) criteria, our final set of included trials amounted to 21. In the following we present an analysis of the technologies in trial on the 21 included trials.

Table 2: Included clinical trials

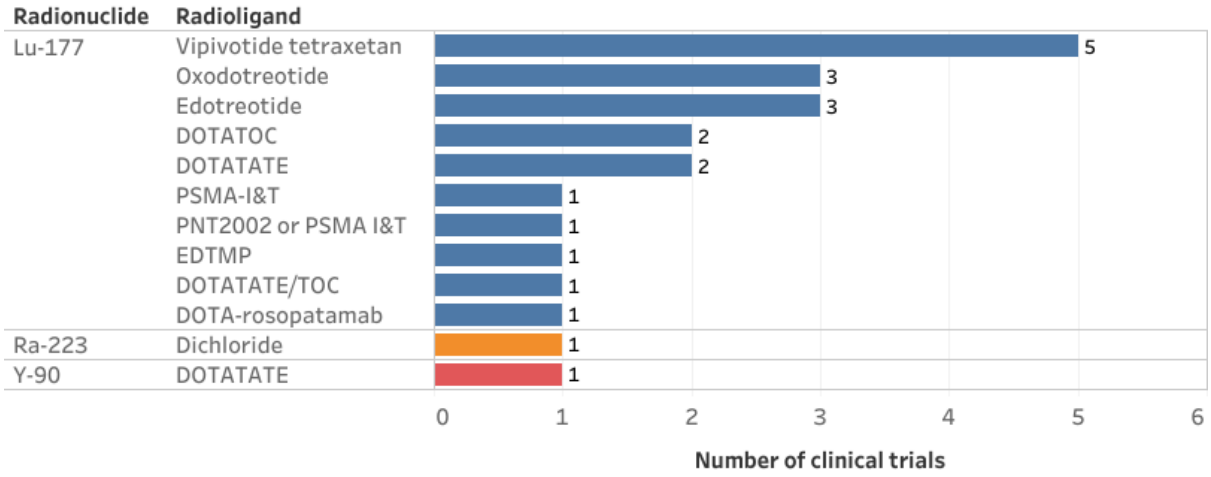
NCT Number	Radionuclide	Radioligand	Sponsor
NCT05701241	Lu-177	Oxodotreotide	University Hospital, Antwerp
NCT04647526	Lu-177	PNT2002 or PSMA I&T	Point Biopharma
NCT05204927	Lu-177	PSMA-I&T	Curium US LLC
NCT04919226	Lu-177	Edotreotide	ITM Solucin GmbH
NCT04876651	Lu-177	DOTA-rosopatamab	Telix International Pty Ltd
NCT06016855	Lu-177	DOTATATE	Vanderbilt-Ingram Cancer Center
NCT06200103	Lu-177	Vipivotide tetraxetan	Mayo Clinic
NCT05387603	Lu-177	DOTATOC	Lund University Hospital
NCT04597125	Ra-223	Dichloride	Bayer
NCT05884255	Lu-177	Oxodotreotide	Jiangsu HengRui Medicine Co., Ltd.
NCT05939414	Lu-177	Vipivotide tetraxetan	Novartis Pharmaceuticals
NCT04689828	Lu-177	Vipivotide tetraxetan	Novartis Pharmaceuticals
NCT05459844	Lu-177	Oxodotreotide	Sinotau Pharmaceutical Group
NCT05477576	Lu-177	DOTATATE/TOC	RayzeBio, Inc.
NCT04720157	Lu-177	Vipivotide tetraxetan	Novartis Pharmaceuticals
NCT05803941	Lu-177	Vipivotide tetraxetan	Novartis Pharmaceuticals
NCT05918302	Lu-177	Edotreotide	Grupo Espanol de Tumores Neuroendocrinos
EUCTR2020-006068-99-PL	Lu-177, Y-90	DOTATATE	National Centre for Nuclear Reseach Radioisotope Centre POLATOM
CTRI/2021/04/033060	Lu-177	EDTMP	AIIMS Jodhpur
EUCTR2021-002218-15-SE	Lu-177	DOTATOC	Region SkÃ¥ne
EUCTR2021-001086-20-ES	Lu-177	Edotreotide	ITM Solucin GmbH

Product Pipeline analysis

Three radionuclides, Lu177, Ra-223, and Y-90, were being investigated across 21 clinical trials. Out of the 21 clinical trials identified, 20 were investigating Lu-177 (Figure 1). I-131, Ra-223 and Y-90 were being investigated in one clinical trial each. One clinical trial was testing both Lu-177 and Y-90. Lu-177 is one of the radionuclides already licensed in combination with a

few specific radioligands in the UK for clinical use and might explain the volume of clinical trials investigated it. The use of Lu-177 as a radionuclide offers potential benefits such as its long half-life, and lack of volatility which allows for sustained radiation therapy.[10] Additionally, the efficacy of Lu-177 in treating certain types of cancer has sparked interest in further research and development.

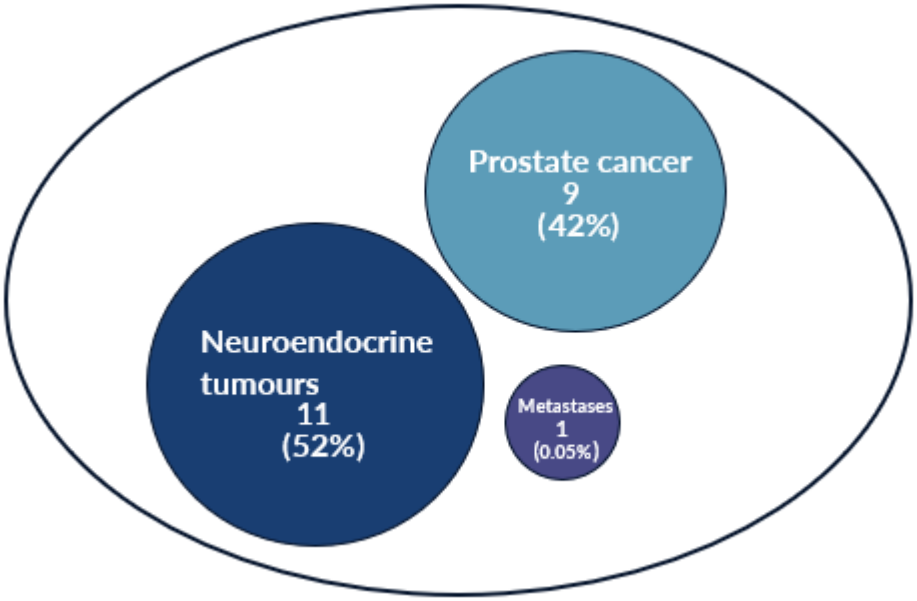
Figure 1: Number of ongoing clinical trials for therapeutic radioligands



Therapeutic Area Landscape analysis

All radioligand technologies were being investigated for cancer indications. Within these, NETs were being assessed the most, followed by prostate cancer. NETs are of particular interest in cancer research due to their unique characteristics. These tumours arise from hormone-producing cells and can occur in various parts of the body, such as the pancreas, lungs, and gastrointestinal tract. Studying NETs can provide valuable insights into the underlying mechanisms of cancer development and help in the development of targeted therapies for not only NETs but also other types of cancer.[11] In addition to NETs, thyroid cancer, pancreatic cancer, and metastatic disease each had one clinical trial where they were being investigated.

Figure 2: Number of clinical trials for indications in clinical development for therapeutic radioligand technologies



Clinical Trial Landscape analysis

In terms of phase of clinical development, most of the clinical trials were in phase 3 (16, 76%) while a small proportion were in phase 4 (5, 24%). No clinical trials included in the final scan were in phase 2/3.

Figure 3a: Number of clinical trials in different stages of clinical development for therapeutic radioligand technologies

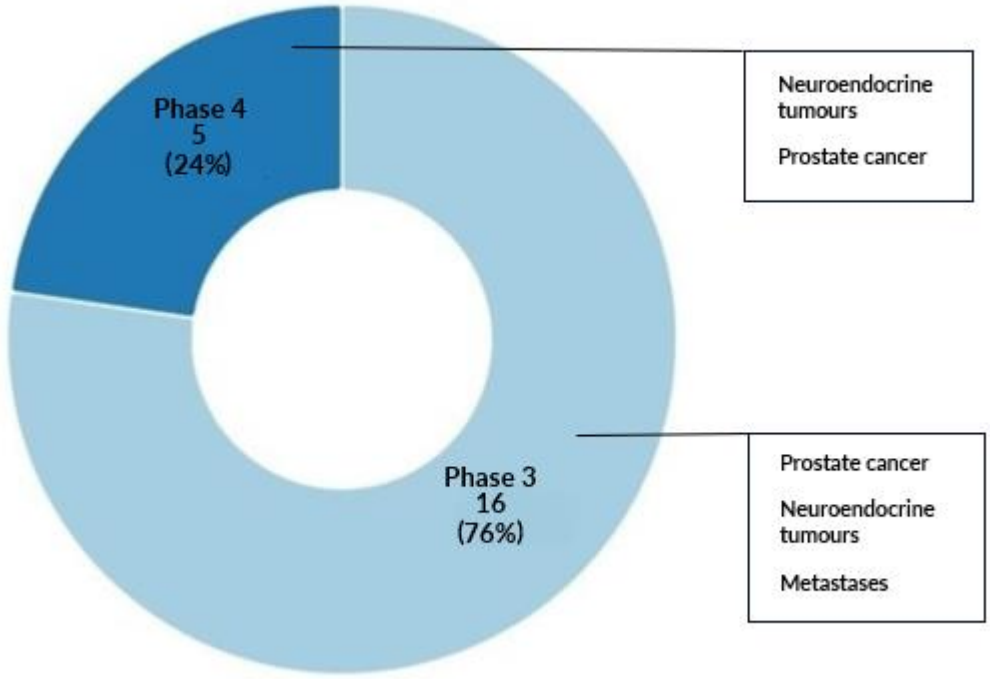


Figure 3b: Number of clinical trials in phase 3 stage of clinical development for therapeutic radioligand technologies

Radionuclide	Ligand	Condition	Location	UK Locations	Sponsor	Primary Completion Date	
Lu-177	DOTA-rosopatamab	Prostate cancer	Not available	No	Telix International Pty Ltd	2025-06	1
	DOTATATE/TOC	Other cancers - NET	Global	No	RayzeBio, Inc.	2025-07	1
	DOTATOC	Other cancers - NET	Europe	No	Lund University Hospital	2025-10	1
					Region SkÃ¥ne	Not available	1
	Edotreotide	Other cancers - NET	Europe	No	Grupo Espanol de Tumores Neuroendocrinos	2028-03	1
			Global	Yes	ITM Solucin GmbH	Not available	1
						2024-09	1
	EDTMP	Metastases	Asia	No	AIIMS Jodhpur	Not available	1
	Oxodotreotide	Other cancers - NET	Asia	No	Jiangsu HengRui Medicine Co., Ltd.	2026-12	1
					Sinotau Pharmaceutical Group	2024-12	1
	PNT2002 or PSMA I&T	Prostate cancer	Global	Yes	POINT Biopharma	2023-12	1
	PSMA-I&T	Prostate cancer	Global	No	Curium US LLC	2024-01	1
	Vipivotide tetraxetan	Prostate cancer	Global	Yes	Novartis Pharmaceuticals	2025-07	1
						2022-10	1
			Not available	No	Novartis Pharmaceuticals	2028-01	1
Lu-177, Y-90	Dotatate	Other cancers - NET	Europe	No	POLATOM	Not available	1

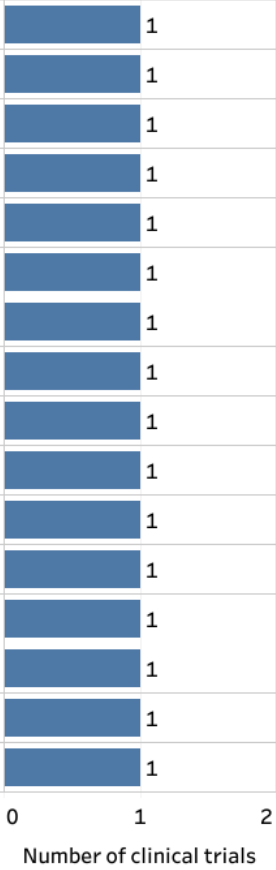
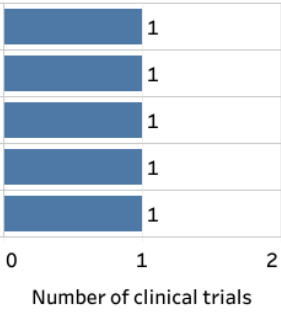


Figure 3c: Number of clinical trials in phase 4 stage of clinical development for therapeutic radioligand technologies

Radionuclide	Ligand	Condition	Location	UK Locations	Sponsor	Primary Completion Date
Lu-177	Dotatate	Other cancers - NET	North America	No	Vanderbilt-Ingram Cancer Center	2025-03
	Oxodotreotide	Other cancers - NET	Europe	No	University Hospital, Antwerp	2029-04
	Vipivotide tetraxetan	Prostate cancer	North America	No	Mayo Clinic	2029-12
					Novartis Pharmaceuticals	2033-07
Ra-223	Dichloride	Prostate cancer	Global	Yes	Bayer	2025-05



Among the 16 phase 3 clinical trials, only one clinical trial was testing Y-90, all clinical trials were investigating for Lu-177 (Figure 3b). There were nine radioligands being tested, each being investigated in 1-2 clinical trials. Half of the clinical trials were investigating NETs, the rest were for prostate cancer and metastases. There were seven trials with global trial locations, five of which included UK locations. A majority of the clinical trials were sponsored by industry. The primary completion dates[1] ranged from 2022-2028. Three of the clinical trials had a primary completion date in 2024, four were to complete in 2025, one in 2026, two in 2028. Four of the clinical trials did not have primary completion or study completion dates available.

Out of the five phase 4 clinical trials, only one clinical trial was testing Ra-223, the rest of the clinical trials were investigating for Lu-177 (Figure 3c). There were four radioligands being tested, each being investigated in 1-2 clinical trials. Three clinical trials were investigating prostate cancer, two were for NETs. Three trials had trial locations in North America, one was in Europe, one had global trial locations. Only two clinical trials were sponsored by industry. The primary completion dates for these trials ranged from 2025-2033. Two of the clinical trials had a primary completion date in 2025, two are to complete in 2025, one in 2033.

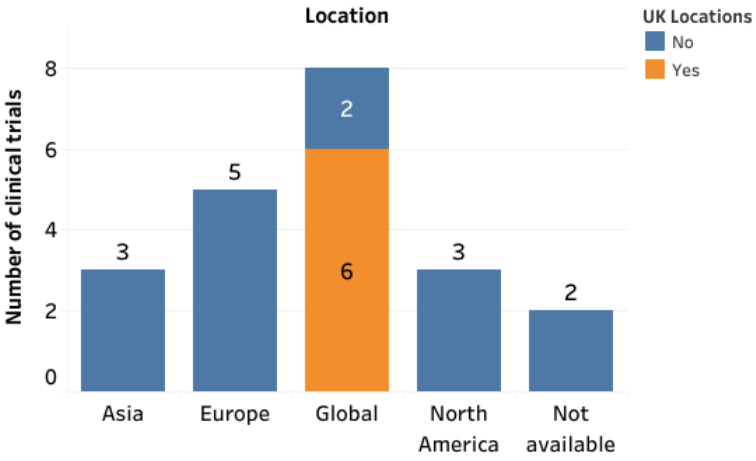
Phase 3 clinical trials are a crucial stage in the development of therapeutic radioligand technologies as they involve a larger number of participants and are designed to assess the safety and effectiveness of the radioligand in a real-world setting. These trials provide valuable data on the potential benefits and risks of the radioligand, helping to determine whether it should be approved for widespread use. Phase 4 clinical trials in radioligand technology research are crucial for evaluating the long-term safety and efficacy of the radioligand. These trials provide valuable data on the radioligand's effectiveness in real-world settings and help identify any potential side effects that may arise over an extended period of use. Additionally, phase 4 trials can also contribute to expanding the range of indications for which the radioligand can be used.

[1] The date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome.

Trial location

More than half of the clinical trials for assessing therapeutic radioligand technologies were being conducted in Europe or global trial locations half of which included European trial locations (Figure 4). UK was included in the trial locations of 6 global clinical trials.

Figure 4: Locations of clinical trials investigating therapeutic radioligand technologies



Sponsor Information

In terms of sponsorship, 13 (62%) clinical trials were sponsored by industry, and 8 (38%) by non-industry sponsors (Figure 5). These results suggest that industry sponsors are more likely to fund clinical trials. Table 3 further summarises which of the various radionuclides under investigation are sponsored by industry and non-industry respectively.

Figure 5: Type of sponsors in clinical trials

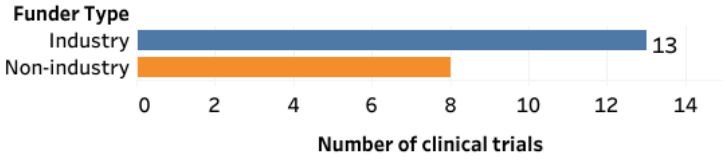


Table 3: List of radionuclides under investigation by sponsors identified from the clinical trial analysis

Sponsor	Radionuclide	Sponsor Type
AIIMS Jodhpur	Lu-177	Non-industry
Antwerp University Hospital	Lu-177	Non-industry
Bayer	Ra-223	Industry
Curium Pharma	Lu-177	Industry
ITM Solucin GmbH	Lu-177	Industry
Jiangsu Hengrui Pharmaceuticals	Lu-177	Industry
Lund University Hospital	Lu-177	Non-industry

Mayo Clinic	Lu-177	Non-industry
National Centre for Nuclear Reseach Radioisotope Centre POLATOM	Lu-177, Y-90	Non-industry
Novartis Pharmaceuticals	Lu-177	Industry
Point Biopharma	Lu-177	Industry
RayzeBio Inc	Lu-177	Industry
Region Skåne	Lu-177	Non-industry
Sinotau Pharmaceutical Group	Lu-177	Industry
Spanish Group of Neuroendocrine and Endocrine Tumors	Lu-177	Non-industry
Telix Pharmaceuticals	Lu-177	Industry
Vanderbilt-Ingram Cancer Center	Lu-177	Non-industry

Among industry sponsors investigating therapeutic radioligand technologies, Novartis and ITM Solucin GmbH appear to be slightly more active in clinical development in the field. ITM Solucin GmBH has two ongoing trials for Lu-177 edotreotide while Novartis has 4 trials for Lu-177 vipivotide tetraxetan. There are 4 companies (RayzeBio, Inc, ITM Solucin GmBH, Jiangsu HengRui MedicinesCo., Ltd, and Sinotau Pharmaceutical Group) assessing Lu-177 for NETs. Five companies (Bayer, Telix International Pty Ltd, Point Biopharma, Curium US LLC, and Novartis Pharmaceuticals) are investigating prostate cancer. All pharmaceutical companies appear to be investigating different therapeutic radioligand technologies. All pharmaceutical companies are investigating Lu-177 apart from Bayer that is assessing Ra-223. Table 4 further summarises the various radionuclides under investigation by industry sponsors, as well as the number and locations of those clinical trials conducted by each industry sponsor. Only Bayer is conducting a clinical trial for Ra-223 dichloride for prostate cancer.

Table 4: Number of clinical trials for each radionuclide, radioligand and indication sponsored by industry

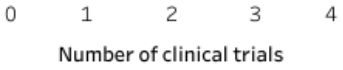
Indication	Radionuclide	Radioligand	Location	
Other cancers - NET	Lu-177	DOTATATE/TOC	Global	1
		Edotreotide	Global	2
		Oxodotreotide	Asia	2
Prostate cancer	Lu-177	DOTA-rosopatamab	Not available	1
		PNT2002 or PSMA I&T	Global	1
		PSMA-I&T	Global	1
		Vipivotide tetraxetan	Global	2
			North America	1
			Not available	1
	Ra-223	Dichloride	Global	1

Regulatory information

The analysis revealed 3 radionuclides and 11 radioligands in our scan. Among these we found two ligands, oxodotreotide and vipivotide tetraxetan, radiolabelled with Lu-177, are licensed by the MHRA (Figure 7) for NETs and prostate cancer respectively. Dichloride radiolabelled with Ra-223 is also licensed by the MHRA for bone metastases from metastatic castration resistant prostate cancer. We also identified clinical trials for Lu-177 vipivotide tetraxetan where either the indication or line of treatment was slightly different from the approved indication (NCT05803941[20], NCT05939414[21], NCT04720157[22]).

Figure 7: Regulatory status of radioligands

Radionuclide	Radioligand	Indication	Regulatory status	Number of clinical trials
Lu-177	DOTA-rosopatamab	Prostate cancer	Not licensed	1
	DOTATATE	Other cancers - NET	Not licensed	2
	DOTATATE/TOC	Other cancers - NET	Not licensed	1
	DOTATOC	Other cancers - NET	Not licensed	2
	Edotreotide	Other cancers - NET	Not licensed	3
	EDTMP	Metastases	Not licensed	1
	Oxodotreotide	Other cancers - NET	Licensed	3
	PNT2002 or PSMA I&T	Prostate cancer	Not licensed	1
	PSMA-I&T	Prostate cancer	Not licensed	1
	Vipivotide tetraxetan	Prostate cancer	Not licensed	3
			Licensed	2
Ra-223	Dichloride	Prostate cancer	Licensed	1
Y-90	DOTATATE	Other cancers - NET	Not licensed	1



The licensing of therapeutic radioligand technologies by the MHRA signifies that these specific ligands, oxodotreotide and vipvotide tetraxetan, radiolabelled with Lu177, have met the necessary safety and efficacy standards set by the regulatory authority. This certification ensures that healthcare professionals can confidently use these radioligands in their therapeutic interventions, providing patients with effective and approved treatment options. If a manufacturer other than the one who currently holds the license wants to manufacture an approved radiopharmaceutical, they would need to apply for an MHRA licence.

Figure 8 shows which of the therapeutic radioligand technologies that are licensed in figure 7 have a published guidance by National Institute for Health and Care Excellence (NICE). Having published NICE guidance for therapeutic radioligand technologies indicates that these treatments have undergone a rigorous evaluation process and have been deemed safe and effective for use in clinical practice. This guidance provides healthcare professionals with valuable information on the appropriate use of these radioligands, ensuring that patients receive the best possible care and outcomes.

Lu-177 oxodotreotide has been recommended by NICE for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic (GEP) NETs[12] which appears to align with one identified trial, (NCT05701241),[13] that is also for metastatic well-differentiated (grade1 or 2) GEP NETs. We

identified two trials (NCT05884255,[14] NCT05459844[15]) for Lu-177 oxodotreotide given in combination with octreotide for inoperable, progressive, well differentiated, GEP NETs. NICE appears to have a guidance in development for this combination, and indication quite similar to this trial.[16]

Out of the five clinical trials identified for Lu-177 vipivotide tetraxetan for prostate cancer, two (NCT06200103,[17] NCT04689828[18]) clinical trials were for PSMA-positive metastatic castration resistant prostate cancer after 2 or more treatments. One (NCT05803941[20]) clinical trial was in phase 4 trial for prostate cancer. As mentioned before in this report, phase 4 clincial trials are crucial for evaluating the long-term safety and efficacy of the radioligand following marketing of a technology. In November 2023, NICE advised that the use of Lu-177 vipivotide tetraxetan for treating PSMA-positive hormone relapsed metastatic prostate cancer after 2 or more treatments[19] was not recommended. This indication seems to align with the trials mentioned above. The other two clinical trials (NCT05939414[21], NCT04720157[22]) were for PSMA positive oligometastatic prostate cancer, and metastatic hormone sensitive prostate cancer.

Figure 8: *NICE appraisal stage of therapeutic radioligands*

Radionuclide	Radioligand	Indication	NICE appraisal stage	Date of NICE recommendation	Number of trials
Lu-177	DOTA-rosopatamab	Prostate cancer	N/A	N/A	1
	DOTATATE	Other cancers - NET	N/A	N/A	2
	DOTATATE/TOC	Other cancers - NET	N/A	N/A	1
	DOTATOC	Other cancers - NET	N/A	N/A	2
	Edotreotide	Other cancers - NET	N/A	N/A	3
	EDTMP	Metastases	N/A	N/A	1
	Oxodotreotide	Other cancers - NET	Awaiting development	TBC	2
			Recommended	Aug-2018	1
	PNT2002 or PSMA I&T	Prostate cancer	N/A	N/A	1
	PSMA-I&T	Prostate cancer	N/A	N/A	1
	Vipivotide tetraxetan	Prostate cancer	N/A	N/A	2
			Not recommended	Nov-2023	3
Ra-223	Dichloride	Prostate cancer	Recommended	Sep-2016	1
Y-90	DOTATATE	Other cancers - NET	N/A	N/A	1

Number of trials: 1 – 3

Terminated, withdrawn, suspended clinical trials

Following the analysis presented above, we carried out an additional analysis on the terminated, withdrawn, suspended clinical trials identified in the initial searches but excluded based on the criteria set by the MRT team. Clinical trials that were in phase 2/3-4 of development were analysed. There were 5 radionuclides, 3 of which were consistent with the ones included in the scan (Lu-177, Ra-223, and Y-90). Among these Lu-177 DOTATATE and Ra-223 dichloride were also found in the data from the final included clinical trials presented above. The rest of the radioligands shown in table 4 were unique.

Table 5: Number of terminated, withdrawn, and suspended clinical trials

Radionuclide	Radioligand	Indication	Study Stat..	Reason for Termination/Suspension	
I-131	Tositumomab	Blood and bone marrow cancers	Terminated	Lack of FDA approval	1
			Withdrawn	N/A	1
In-111	Pentetréotide	Metastases	Terminated	Poor enrolment	1
Lu-177	Dotatate	Other - NET	Withdrawn	N/A	1
Ra-223	Dichloride	Prostate cancer	Terminated	Due to the changes of standard of care, and slow recruitment	1
Y-90	Clivatuzumab Tetraxetan	Pancreatic cancer	Terminated	Did not demonstrate a sufficient improvement in overall survival	1
	Ibritumomab tiuxetan	Blood and bone marrow cancers	Terminated	Business decision	1
				Poor enrolment	1

As can be seen in the table 5 above, there are a number of reasons why clinical trials of therapeutic radioligand technologies are terminated or withdrawn, including poor enrolment, business decision, and lack of FDA support. Business decisions can have a significant impact on the success of clinical trials for therapeutic radioligand technologies. These decisions, which may be influenced by financial considerations or changes in strategic direction, can lead to the termination or withdrawal of support for clinical trials, even if the research shows promising results. This can be frustrating for researchers and patients alike, as it hinders the progress and potential benefits of therapeutic radioligand technologies.

Additionally, the termination may discourage future investment and collaboration in similar research endeavours, leading to a slowdown in advancements in the field of radionuclide imaging and therapy.

Discussion

We identified 3 radionuclides and 11 therapeutic radioligand technologies in our scan. Most of the clinical trials identified for therapeutic radioligand technologies were for Lu-177. We identified 3 radioligands within the scan that had been licensed by the MHRA that are given in clinical practice after being radiolabelled with either Lu-177 or Ra-223. Therapeutic radioligand technologies identified in terminated/suspended/withdrawn clinical trials were slightly more distributed among Lu-177, Ra-223, In111, I-131, and Y-90 which were excluded from the scan.

The results of our scan indicate that there is not much development that could result in an immediate change in clinical pathways in the United Kingdom. There were 4 phase 3 clinical trials investigating new therapeutic radioligand technologies where UK was among the trial locations. All of these clinical trials had study completion dates in 2026 and beyond. One phase 3 clinical trial in Sweden for Lu-177 DOTATOC that was scheduled to complete in October 2025, which might be the only potential disruption to planning and preparation by regulatory authorities such as the MHRA or designated bodies such as NICE.[23] Nevertheless, we identified

the sponsor for this trial as a non-industry entity. To ascertain if this would eventually be brought to the UK market, it is essential to know which pharmaceutical company is producing Lu-177 DOTATOC in the UK.

We observed a high number of clinical trials in Europe in our analysis which could be due to a few reasons. Firstly, Europe has a well-established and robust regulatory framework for conducting clinical trials, ensuring the safety and ethical standards are met. Additionally, Europe has a diverse population with varying genetic profiles, making it an ideal location for testing the efficacy of radioligands in different patient populations. Finally, Europe also offers a strong network of research institutions and highly skilled healthcare professionals, making it an attractive destination for conducting clinical trials. The inclusion of the UK in global clinical trials highlights the country's importance as a hub for research and development in the field of therapeutic radioligand technologies. It signifies the UK's contribution to advancing medical knowledge and underscores its role in international collaboration and innovation.

Another observation from our scan is that all indications that are being investigated for therapeutic radioligand technologies are cancer indications. The ability to specifically target cancer cells makes therapeutic radioligand technologies an attractive option for cancer treatment. Within cancer indications, we identified two cancer conditions namely, NETs, and prostate cancer, along with metastases. We investigated the type of indications being assessed in terminated/suspended/withdrawn clinical trials. Theses clinical trials also appeared to be focussed on cancer indications. We found two new cancer indications in the terminated/suspended/withdrawn clinical trials, blood cancers and pancreatic cancer.

There could be several reasons for the lack of non-cancer indications in therapeutic radioligand technologies. One possibility is that the mechanism of action of these technologies is better suited for targeting cancer cells specifically. Another reason could be that non-cancer indications have not been extensively studied yet, and further research is needed to determine their effectiveness. By conducting further research on non-cancer indications for therapeutic radioligand technologies, we may discover new and potentially effective treatment options for a wide range of diseases and conditions. This could lead to improved patient outcomes, expanded therapeutic options, and advancements in medical science. Additionally, exploring the potential benefits of therapeutic radioligand technologies in non-cancer indications may open up new avenues for innovation and development in the field of targeted therapy.

Conclusion

To date, the use of therapeutic radioligand technologies to treat cancer has mainly been limited to a small number of niche indications, such as thyroid cancer and NETs. According to Wadsley and Flux, in the last decade there has been a rapid increase in the number of publications relating to the use of therapeutic radioligand technologies across a range of cancers, including colorectal, hepatocellular, breast, and prostate. However, therapeutic radioligand technologies are still only delivered by a relatively small number of centres. This rapid growth presents challenges for service delivery and healthcare economics at a national scale.[1]

Our scan shows that while there is substantial interest in therapeutic radioligand technologies, there is limited ongoing late-stage clinical development. Additionally, this is limited to a few therapeutic radioligand technologies radiolabelled with Lu-177, Ra-223, and Y-90, mainly for prostate cancer and NETs. Engagement with pharmaceutical companies manufacturing these radioligand technologies is essential to ascertain, which of the above therapeutic radioligand technologies would be brought to the UK for clinical use in the NHS.

Our global horizon scan provides not only the All-Wales MRT team, but also other national organisations/bodies, with information on the opportunities for discovering new indications for therapeutic radioligand technologies of interest. The knowledge of these new and upcoming clinical indications of interest and radioligands could support in future planning for inclusion of therapeutic radioligand technologies currently in use for other indications. It will also allow health organisations to prepare for the adoption of new therapeutic radioligand technologies in clinical use.

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Appendix 1. Clinical studies search strategy

Source	Search terms	Number of clinical trials downloaded	Number of clinical trials sifted	Number of trials included
Clinicaltrials.gov	Radionuclide	639	60	
	Therapeutic radiopharmaceutical	791		
	Radiolabelled	574		
	Theranostic	71		
	Theragnostic	14		
	P-32 OR phosphorus-32 OR "phosphorus 32" OR Y-90 OR yitrium-90 OR "yitrium 90" OR I-131 OR iodine-131 OR "iodine 131" OR Ho-166 OR holmium-166 OR "holmium 166" OR Lu-177 OR lutetium-177 OR "lutetium 177" OR Ra-223 OR radium-223 OR "radium 223" OR Ac-225 OR actinium-225 OR "actinium 225" OR Th-227 OR thorium-227 OR "thorium 227"	663		
ICTRP	Y-90 or yttrium-90	149	20	
	Ac-225 or actinium-225	10		
	I-131 or iodine-131	206		

	Lu-177 or lutetium-177	106		
	P-32 or phaosphorus-32	7		
	Ra-223 or radium-223	150		
	Radiolabelled	90		
	Radionuclide or Radioisotope	272		
	Th-227 or thorium-227	3		
	Therapeutic radiopharmaceutical	15		
Total		3,760	80	22

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