EXECUTIVE INSIGHTS

From Niche to Widespread Use: The Turning Point for Radiotherapeutics

Key takeaways

1. Radiopharmaceuticals have the potential to transition to mainstream use, driven by their dual role in diagnostics and therapy, especially in oncology.
2. Recent commercial success with beta-emitting treatments like Lutathera and Pluvicto signal strong growth, while a rich overall pipeline increasingly diversifies towards emerging alpha-emitting isotopes and novel ligand targets.
3. Biopharma companies interested in radiotherapeutics need to carefully assess investment in the right innovation areas – potentially via M&A – alongside a subsequent build of a broader radiotherapeutics presence.
4. To support a successful launch, biopharma must consider commercial capability build-out and decide whether to in-house or outsource often complex supply chain and manufacturing.

Radiopharmaceuticals are seeing increased use across diagnosis and treatment

Radiopharmaceuticals are a rapidly advancing class of compounds used for diagnosis and treatment in oncology and other therapeutic areas. Their dual capabilities in imaging and therapy have attracted substantial pipeline development and recent M&A interest. As companies seek to capitalise on precision medicine, radiopharmaceuticals have the potential to move to widespread use.

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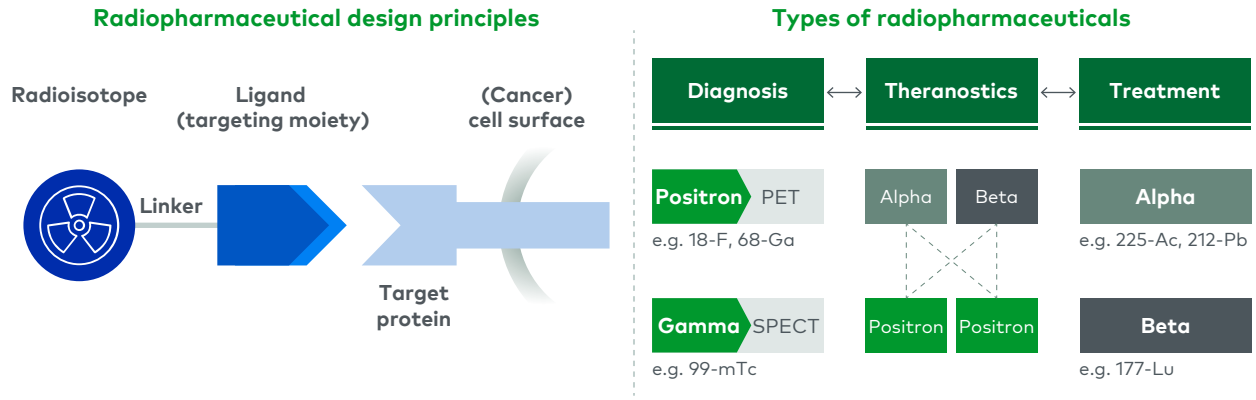
Radiopharmaceutical compounds rely on the combination of a radioactive isotope and a linked ligand (targeting moiety) which helps direct the isotope to specific cells within the body that express the marker of interest (see Figure 1).

Figure 1

Radiopharmaceutical design principles and types of radiopharmaceuticals



Note: PET=positron emission tomography, SPECT=single photon emission computed tomography
Source: L.E.K. research and analysis of company investor materials, press releases and industry reports

In diagnostics, isotopes must emit rays that can travel out of the patient to be imaged and that have a half-life suitable for decay within hours following imaging. PET (positron emission tomography) and SPECT (single photon emission computed tomography) are leading techniques. PET uses positron-emitting isotopes like 18-F, providing high-resolution, 3D images essential for early diagnosis and monitoring of progression. SPECT, employing gamma-emitting isotopes like 99-mTc, offers an accessible yet lower-resolution alternative. The higher resolution offered through PET is commonly used for functional imaging of cancer and brain disorders, while more widely available and cost-effective SPECT sees use in cardiac imaging.

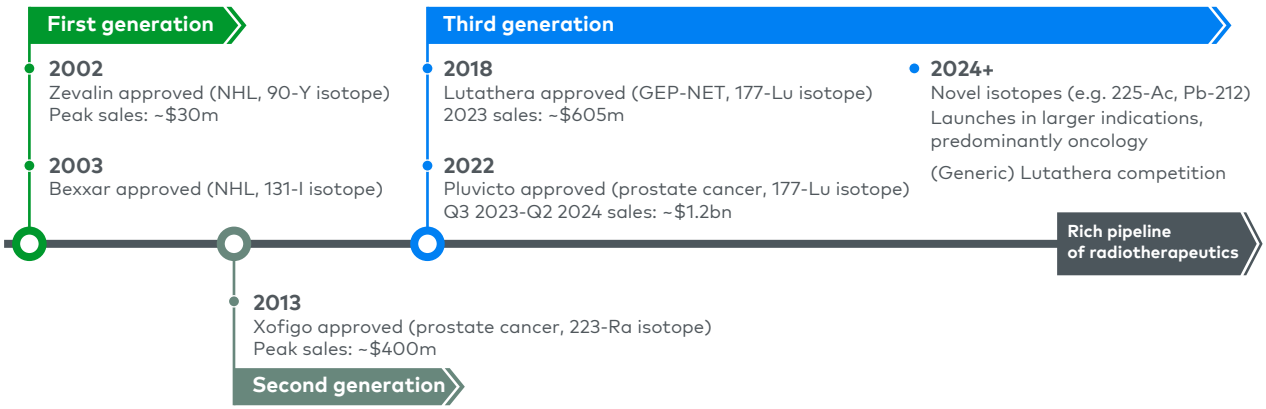
In therapeutics, direct delivery to tumour cells minimises damage to healthy tissue throughout the body. Damage to surrounding tissue is minimised by the short tissue penetration of the alpha and beta particles. This contrasts with radiosensitisers, which are non-radioactive agents that aim to make tumours more susceptible to external radiation therapy (e.g. NBTXR3, AGuIX). Treatment with radiopharmaceuticals can be achieved through alpha- and beta-emitting isotopes. Alpha-emitters (e.g. 225-Ac) deliver highly localised radiation and are ideal for targeting small clusters of cancer cells but are an emerging and less proven treatment option. Conversely, beta-emitters (e.g. 177-Lu) penetrate tissue further with lower energy, treating larger or more diffuse tumours, and are more established.

Radiotherapeutics have historically faced an uphill battle (see Figure 2). First-generation approvals faced substantial commercial challenges. Zevalin (2002, 90-Y isotope) and Bexxar (2003, 131-I isotope), launched in non-Hodgkin lymphoma, relied on isotopes with a relatively short half-life of around 2.7 days and central manufacturing sites posing geographical barriers on addressable patient populations. Physician preference for Rituxan further limited market penetration.

Xofigo (2013, 223-Ra) was the first alpha-emitter to enter the market in 2013. While it addressed many of the first-generation limitations, it has never lived up to its commercial promise of $1.5bn peak sales despite its perceived high efficacy and targeting specificity in late-stage prostate cancer – instead peaking at around $400m.[1] The asset suffered from safety concerns in combination with J&J's Zytiga and the emergence of novel non-radiotherapy options.

Figure 2

Resurgence following initial hurdles



Note: NHL=non-Hodgkin lymphoma, GEP-NET=gastroenteropancreatic neuroendocrine tumour
Source: L.E.K. research and analysis of company investor materials, press releases and industry reports

From initial hurdles to resurgence in radiotherapeutics development

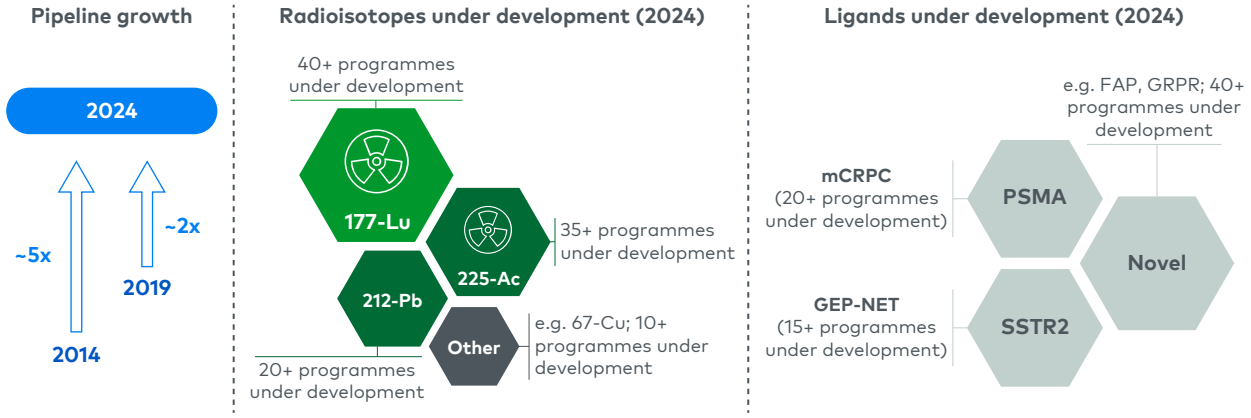
Clear commercial successes have been achieved more recently with beta-emitting 177-Lu compounds, predominantly through Novartis in mCRPC (Pluvicto, 2022) and GEP-NET (Lutathera, 2018). Pluvicto reached $345m in Q2 2024 sales,[2] with analysts expecting blockbuster status reaching close to $2bn by 2026F,[3] particularly as temporary supply constraints observed in 2022 and 2023 have been resolved with the opening of a fourth manufacturing site in Indianapolis, Indiana, in early 2024.

The recent clinical and commercial validation and the upcoming loss of exclusivity of Lutathera have spurred further sector interest. The therapeutics pipeline is particularly healthy, with over 100 programmes in development as of September 2024 (see Figure 3); the pipeline has

doubled over the past five years. Focus remains largely on oncology indications, contrary to diagnostics – where cardiology and neurology are key additional therapeutic areas.

Figure 3

Rich pipeline increasingly diversifying towards novel isotopes and targets



Note: mCRPC=metastatic castration-resistant prostate cancer, GEP-NET=gastroenteropancreatic neuroendocrine tumour, FAP=fibroblast activation protein, GRPR=gastrin-releasing peptide receptor, PSMA=prostate specific membrane antigen, SSTR2=somatostatin receptor 2
Source: L.E.K. research and analysis of company investor materials, press releases and industry reports

For beta-therapies, 177-Lu sees large late-stage activity, partially driven by the development of generic alternatives to Lutathera; multiple entrants submitted applications for approval in H1 2024. Copper-67 (67-Cu) provides a lesser-proven alternative isotope that mostly sees activity in early-stage Phase I/II development combined with de-risked ligands trialled with 177-Lu assets (e.g. PSMA, SSTR).

For alpha therapies, discussion around the optimal isotope is continuing. Despite Xofigo's first 223-Ra launch, research activity had gravitated towards 225-Ac with pipeline assets positioned as the next wave behind 177-Lu. Interest is driven by its roughly 10-day half-life and relatively manageable ability to be linked to targeting moieties. 212-Pb is, however, increasing in popularity among investigators, where a substantially shorter half-life of around 10 hours opens the possibility for optimising a dosing schedule through administration of a lower number of larger doses (fractionation) as well as balancing of adverse exposure to healthy tissue while achieving a therapeutic effect.

The industry is expanding its interest beyond PSMA and SSTR targeting ligands with the emergence of novel targets for other predominantly oncology indications. In particular, FAP (fibroblast activation protein) has seen early-stage development activity due to its theranostic potential across tumour types.

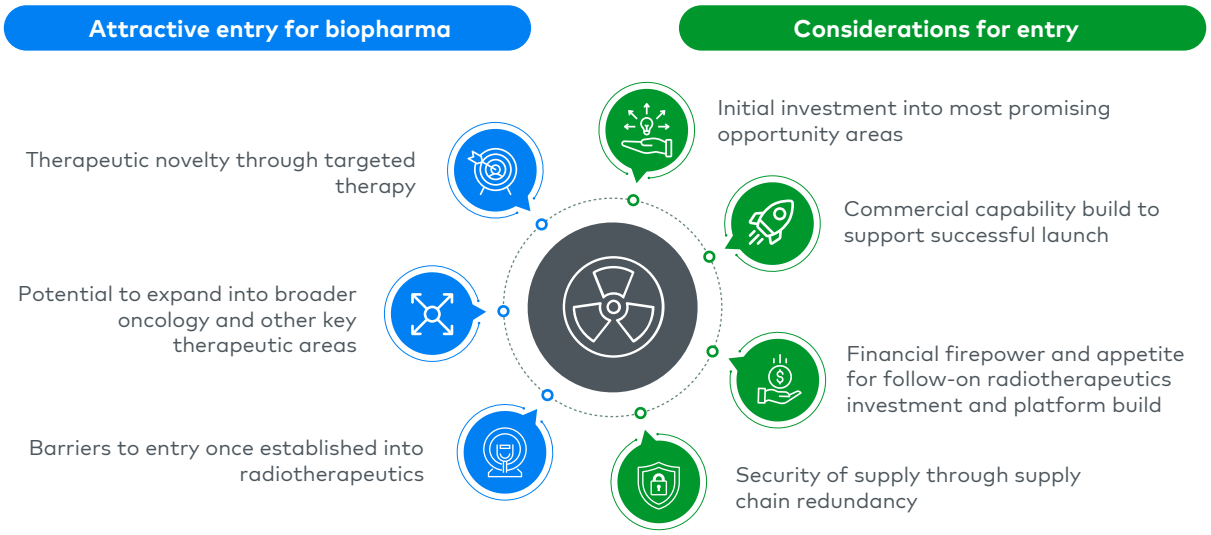
Key considerations for biopharma assessing potential entry into radiotherapeutics

As the radiopharmaceuticals sector is experiencing unprecedented interest, biopharma will need to consider key elements to succeed (see Figure 4). Initial investment in the right innovation areas – by isotope, ligand, therapeutic indication – should be carefully assessed, in addition to follow-on investment to build a broader radiotherapeutics platform. To support a successful launch, consideration must be given to commercial capability build-out, as well as decision-making regarding whether to in-house or outsource manufacturing, which itself can be quite complex. Notably, the shorter half-life of some of these radioisotopes (i.e. those that are measured in hours) will require different manufacturing and supply chain infrastructure that could significantly impact operations and financials.

M&A offers biopharma an accelerated path into radiotherapeutics and has been a preferred route in recent years for big pharma. Novartis, AstraZeneca, Bristol Myers Squibb and Eli Lilly were responsible for four of six key radiotherapeutics acquisitions announced since February 2023, with a total deal value equalling $8.6bn. Other big pharma companies, such as Sanofi, are increasing exposure to radiotherapeutics through agreements with early-stage private companies.[4]

Figure 4

Considerations for biopharma entry into radiotherapeutics



Source: L.E.K. research and analysis

M&A substrate continues to grow, as pipeline growth has been underpinned by a rising number of biotechs dedicating R&D investment. We have tracked over 70 companies with an active pipeline portfolio of radiotherapy assets. Around two-thirds are privately held, with a geographical split roughly equal between North America, Europe and Asia-Pacific.

Public small-/mid-cap companies have some cash runway, with median cash on hand at around $20m and median enterprise value at roughly $125m. Public funding surged in 2020 and 2021 due to several IPOs (e.g. Clarity Pharmaceuticals) and has since continued at a more moderate pace, with RayzeBio's IPO in 2023 as a notable exception. Similarly, private companies have typically seen a median $40m-$50m Series A or B investment as recently as the last two or three years. In 2023, radiopharmaceutical companies raised close to $1bn in private funding. These earlier-stage companies are typically driving research in novel ligands beyond PSMA and SSTR.

Selection of the right M&A target for established pharma needs to consider both the clinical and commercial potential of the portfolio as well as the target's supply chain and manufacturing capabilities. Securing redundancy in supply chains is apparent from partnership activity, with four supply partnerships between isotope suppliers and biopharma announced from January to April 2024 alone.

Biopharma will need to decide between in-house versus outsourced manufacturing. Manufacturing and supply chain improvements are likely to remain a topic of discussion and a key area of investment focus. Consideration of isotope half-lives and diverging manufacturing routes (e.g. through generators or particle accelerators) – which provide trade-offs between capital investment, ease of set-up, footprint and expertise required to run – will continue to be an area of diligence.

Conclusion

Ongoing innovation and strategic acquisitions underscore the sector's vitality and promising trajectory, representing a key turning point for radiotherapeutics to transition to more mainstream treatment.

To explore how L.E.K. can help you navigate the opportunities and challenges in radiotherapeutics, please reach out to our team. We can offer strategic guidance to set you up for success in this rapidly evolving space.

Endnotes

[1]Emanuele Ostuni and Martin R G Taylor (2023), "Commercial and business aspects of alpha radioligand therapeutics." Frontiers in Medicine, https://pmc.ncbi.nlm.nih.gov/articles/PMC9932801/#B43

[2]Novartis (2024), "Condensed Interim Financial Report – Supplementary Data." https://www.novartis.com/sites/novartiscom/files/2024-07-interim-financial-report-en.pdf

[3]Fierce Pharma (2023), "Novartis halts Pluvicto new patient starts, struggles with radiotherapy's supply amid manufacturing expansion." https://www.fiercepharma.com/manufacturing/novartis-halts-pluvicto-new-patient-starts-struggles-radiotherapy-supply-amid

[4]Sanofi (2024), "Communiqué de presse : Accord de licence entre Sanofi, RadioMedix et Orano Med pour le développement d'une nouvelle génération de radiothérapies internes vectorisées contre les cancers rares." https://www.sanofi.com/fr/media-room/communiques-de-presse/2024/2024-09-12-05-00-00-2944919; Sanofi (2024), "Communiqué de presse : Sanofi et Orano Med unissent leurs forces pour développer des radiothérapies internes vectorisées de nouvelle generation." https://www.sanofi.com/fr/media-room/communiques-de-presse/2024/2024-10-17-05-30-00-2964590

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