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Key Trends Driving the Emergence of Targeted Radiotherapeutics as an Oncology Therapeutic Pillar

AUTHORED BY

Vikram Gosain, Partner

RESEARCH CONTRIBUTORS

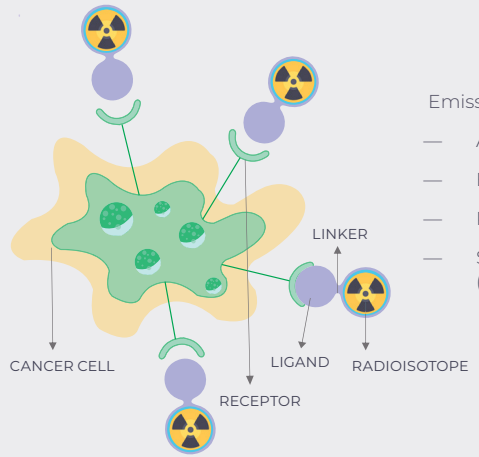
Andris Ortmanis, Sr. Director & Anita Zutshi, Associate Director

Targeted radiopharmaceuticals are transforming cancer treatment by enabling systemically delivered radiotherapy to be integrated into diagnostic workup algorithms and personalized medicine treatment strategies across a range of tumors.

The FDA and EMA have approved two radioligand therapies for the treatment of cancer, LUTATHERA (GEP-NETs) and PLUVICTO (mCRPC). Both agents were acquired by market leader Novartis while in pivotal development and delivered global revenue of $1.8B in 2023. Novartis projects PLUVICTO alone has >$3B global market potential, which underscores the commercial and therapeutic impact of the expanding pipeline of radioligand therapeutics.

Targeted radiopharmaceuticals may become the ultimate focal therapy by enabling the delivery of lethal radiation to malignant tissue – with minimal healthy tissue involvement. The specific structure of a radiopharmaceutical depends on the intended application but consists of a radioisotope payload associated with a small molecule ligand or monoclonal antibody to target malignant tissue.

FIGURE 1: THERAPEUTIC RLTS AND THEIR COMPANION DIAGNOSTIC



Emission type must be suitable for diagnostic imaging or treatment

- Alpha emitters: 211-As (Astatine); 225-Ac; 212-Pb
- Beta emitters: 177-Lu; 161-Tb (terbium); 67-Cu
- PET Imaging (Positron emitters): 68-Ga; 18-F; 64-Cu
- SPECT Imaging (Gamma emitters): 161-Tb (Terbium); 99-Tc (Technetium), 89-Zr (Zirconium)

Figure 1: Therapeutic RLTs and their companion diagnostic counterparts generally only differ in their associated radioisotopes, with either beta (e.g. 177-Lu, 67-Cu, 131-I) or alpha (e.g. 225-Ac, 227-Th) emitters used therapeutically, and positron-emitting radioisotopes (e.g. 68-Ga, 18-F) used for diagnostic purposes. This enables the personalized radiotherapy to be delivered with the same construct that was used to visualize and characterize the tumor diagnostically.

Rich pipeline attracts BD/out-licensing deals with larger partners seeking radiopharmaceutical franchises

As detailed in Table 1, more than 30 innovators, primarily clinical-stage pharmaceutical companies, have advanced >40 assets into the clinical development pipeline. This has attracted leading global pharmaceutical players who have recognized the promise of radiopharmaceuticals to extend their portfolios with these innovative agents, or to supplement in-house radiopharmaceutical franchises with high potential assets.

More than 20 partnering deals have been reported in the last 2 years alone.

- Beyond LUTATHERA and PLUVICTO, Novartis has licensed a FAP targeting construct from German-based 3B Pharmaceuticals and closed a deal with Bicycle Therapeutics to develop protein ligands against oncology targets.
- Bayer has expanded its existing radiopharmaceutical portfolio by acquiring Noria and PSMA Therapeutics to access PSMA (prostate) targeting agents and has entered a strategic collaboration with Bicycle Therapeutics to develop additional agents based on proprietary, synthetic peptide carriers.
- Eli-Lilly completes acquisition of Point BioPharma, accessing PNT2002 and PNT2003 pivotal programs targeting PSMA (mCRPC) and SSTR (GEP-NETs), respectively, and an earlier phase program targeting FAPα (PNT2004).
- BMS also announced the acquisition of a clinical-stage radiopharmaceutical company, RayzeBio, for ~$4.1B. BMS will gain late-stage asset RYZ101, actinium-based RLT (ongoing in SSTR2 expressing GEP-NETs in 177Lu refractory patients), and will also gain access to the manufacturing facility of RayzeBio.
- Telix announces the proposed acquisition of US-based QSAM Biosciences and its lead asset, CycloSam® (Samarium-153-DOTMP), a bone-targeting, beta-emitting radiopharmaceutical with therapeutic implications for bone cancer or bone metastasis.

Table 1 summarizes the intensifying radiopharmaceutical development pipeline, which is largely fueled by clinical-stage biotech companies that are exploiting a growing number of targetable biomarkers across primarily solid tumors. More than 80% of these assets reside in the pipelines of smaller pharmaceutical and clinical-stage biotech companies. As such, they remain potential in-licensing or acquisition targets of “big pharma” as their clinical development matures.

Table 1: Radiopharmaceuticals in clinical development. The highest phase of clinical development for an asset in a tumor has been specified

Targets	Lead Company	Number of Assets	GU			GI						Gynecological				Respiratory		Others						
			Prostate	Urothelial	RCC	Gastric	Esophageal	PDAC	HCC	CCA	CRC	Ovarian	Endometrial	Cervical	Breast	NSCLC	SCLC	SCCHN	Melanoma	Glioma	NETs	Sarcoma	Other Solid Tumors or Unspecified	Heme
Ligand or Small Molecule Carriers																								
PSMA	NVS	14	●																					
SSTR	NVS	6															●				●			
GRPR/1	NVS, Clarity	3	●								●			●	●	●			●		●		●	
FAP	NVS, Eli Lilly	2				●	●	●		●	●							●	●			●	●	
MC1R	Perspective	1																	●					
CAIX	DebioPharm	1			●			●			●													
NTSR1	Fusion	1				●		●			●							●			●	●		
Monoclonal Antibody Carriers																								
PSMA	Telix	4	●																					
HER2	Precirix	2				●	●								●									
HK2	Janssen	1	●																					
CD33	Actinium	1																						●
CD25	Actinium	1																						●
CD37	Nordic Nanovector	1																						●
CAIX	Telix	1			●																			
IGF-1R	Fusion	1										●	●	●	●			●	●					
CDH3	Perseus Proteomics	1						●	●	●	●				●			●						
La/SSB	Telix	1										●				●	●							
FZD10	OncoTherapy	1																				●		
FGFR3	Fusion	1		●		●			●		●	●			●	●		●						
GD2	Y-mAbs	1															●		●			●		

Highest phase of clinical development: ● Phase III ● Phase II ● Phase I/II ● Phase I

INNOVATION AND DEVELOPMENT STRATEGIES DRIVING EMERGING TRENDS

The following table details key development and innovation trends that are expected to drive the adoption and clinical value of radiotherapeutics in oncology. Innovators are modifying the design of constructs to improve their targeting characteristics and to amplify the therapeutic index of these next-generation radiotherapeutics.

Emerging Trends	1 Expansion to address unmet needs across hard-to-treat tumors	2 Improve AE profiles and reduce off-target toxicity	3 Improve efficacy and clinical utility
Key Innovation Drivers	— With clinical and regulatory POC established in GEP-NETs and mCRPC, radiopharmaceutical development has proliferated to span >15 target malignancies across solid and hematologic tumors. — Pipeline radiotherapeutic designs are exploring many novel targets that, to date, have not been leveraged, or are only in very early development by other modalities (e.g., HK2, NTSR1, GRPR1).	— Next-generation targeted radiotherapeutics leverage innovative platforms and vehicles to improve radioisotope targeting to improve efficacy and ameliorate toxicity issues: ▪ Radio DARPin (Designed Ankyrin Repeat Proteins) constructs that are genetically engineered antibody mimetic proteins which exhibit highly specific, high-affinity target protein binding, are expected to reduce uptake by healthy tissues and critical organ systems, such as renal accumulation. ▪ Constructs may exploit differential TME versus health tissue features such as lower pH, greater hypoxia, or specific enzymatic (e.g. protease) activity to activate or enhance ligand/small molecules or mAb-mediated binding avidity. ▪ Single domain antibodies or nanobodies that exhibit shorter relative blood half-life, enhanced uptake by tumors, and have superior binding affinity and specificity for target biomarkers.	— Harnessing the greater lethality of alpha-emitting (versus beta-emitting) radioisotope payloads: ▪ Alpha emitters provide for high energy decay with limited tissue penetrance to deliver potent radiation while minimizing exposure to healthy tissues that do not harbor biomarker targets. ▪ Emergence of alpha-emitting radioisotopes (e.g. 225-Ac, 211-As, 212-Pb) may offset beta emitter demand, but their supply issues parallel those of beta emitters. — Use of alternate beta-emitters such as 67-Cu, 131-I, and 161-Tb will diversify radioisotope sourcing and mitigate potential supply-side pressures for medical- grade components as demand escalates. — Transition from monotherapy regimens to rationally designed, synergy-driven combination use: ▪ DNA repair inhibitors (e.g. PARPi). ▪ Anti-PD-(L)1 agents to leverage the potential of radiotherapy-induced neo-antigens. ▪ Chemotherapeutic agents already established as radiosensitizers in chemoradiation protocols. — Development in earlier lines of therapy following establishment of clinical/regulatory POC (Proof of Concept) in heavily pre-treated disease.

A differentiated radiotherapeutic portfolio will not be enough to win

While having an innovative and differentiated portfolio will be required to stand out versus competition, so too will be the need to address challenges that are specific to radiopharmaceuticals

- Supply chain: Establishing a robust supply chain for high-value substrates such as medical grade isotopes. Radio-decay characteristics and potential supply-side availability in the face of anticipated escalating demand underscores sourcing as a key success factor
- Manufacturing & distribution: Need to optimize manufacturing and distribution through either centralized, localized (third-party radiopharmacies), or mixed approaches to address geography/territory specific challenges.
- Prescriber network: Field medical and sales teams must be realigned or expanded to engage, educate, and support multidisciplinary care teams, including radiation oncologists and treatment centers capable of administering radiopharmaceuticals.

In closing, whether through acquisition or innovation, radiopharmaceutical deal-making and development will intensify in 2024 as emerging clinical evidence further reinforces the paradigm- shifting therapeutic benefit of radiotherapeutics. Will radiotherapeutics see the next round of deal- making frenzy as ADCs? We wouldn't bet against it.

Putnam is a strategic partner to pharmaceutical companies; we offer oncology expertise and commercial development strategies that transform promising radiopharmaceuticals into market leaders.

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