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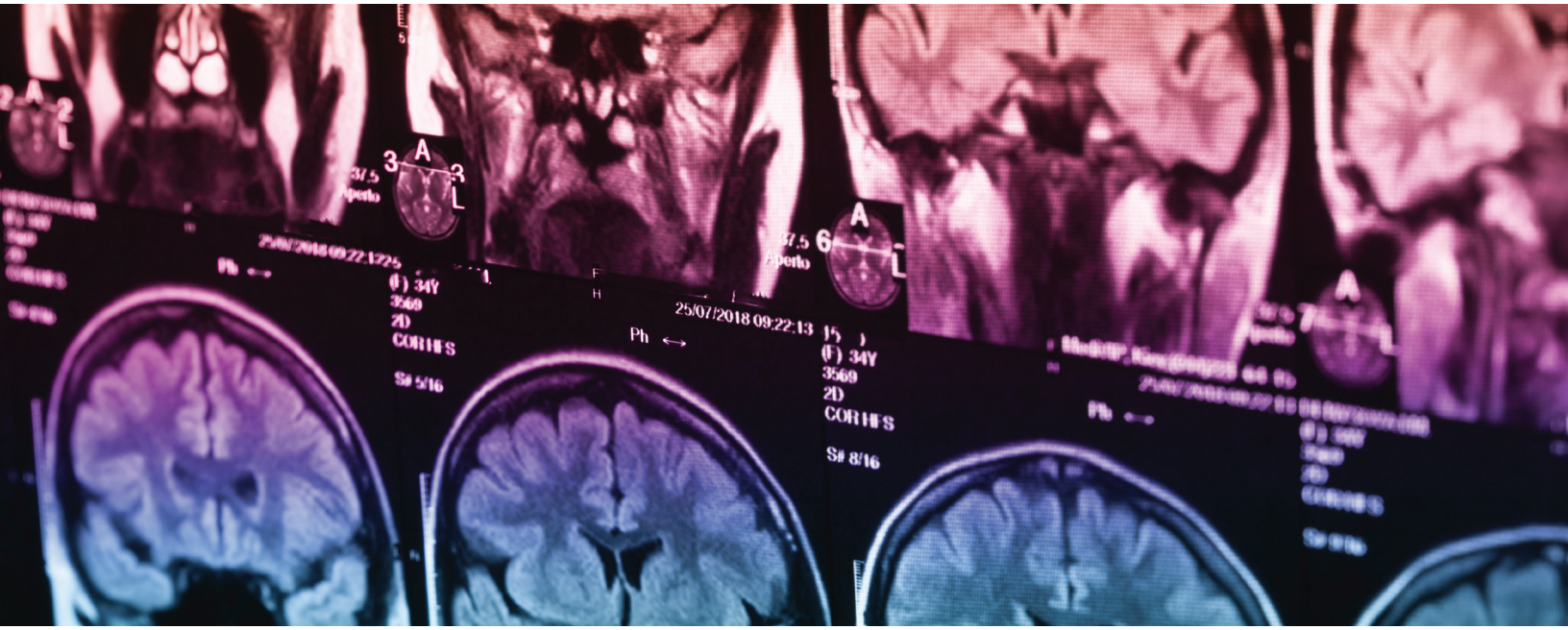
The Radiopharmaceutical Renaissance:
Radiating Hope in Medicine



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Abstract

The use of radiation to identify and/or treat disease has long been a tool within oncologists armamentarium. While first-generation targeted radiopharmaceutical products struggled commercially, the advent of more effective, safer, and easier use molecules has spurred a renewal in the field that has consummated in a flurry of recent licensing, M&A, and VC activity. Given this industry interest, we assessed the transactional and investment landscape within the radiopharma space over the past 5 years, spanning therapeutics, diagnostics, and theranostics. 2022 was a watershed year for the space with 25 strategic transactions and $527M invested from the VC community. Despite an overall downturn in the biotech market in the 2022-2023 timeframe, the strategic and VC activity within the radiopharmaceutical space has remained relatively strong. Indeed, the average raise for radiopharma sponsors in 2023 was $51M, which eclipsed that of 2022, at $38M. Furthermore, as the use of radiopharmaceuticals to identify and treat tumors becomes increasingly commonplace, there is an increasing focus on bringing these technologies beyond the oncologist. With continued commercial success of launched products and technical advances to improve the efficacy and ease of clinical delivery we expect the interest in the space to continue at pace.

Introduction and Therapeutic Applications

The concept of harnessing radiation to treat tumors dates back as early as the late 1800s and has been utilized ever since by directing external beams of radiation to a tumor within the body.1 The use of systemic radioactive medicines as therapies for cancer were first employed in the 1940s, when physicians utilized radioiodine for the treatment of thyroid cancer. While external radiotherapy and radioisotope therapies were significant advancements in the field, they still suffered from a lack of potency and specificity and were associated with a myriad of negative side effects.

Since then, scientists and clinicians aimed to deliver safer and more potent medicines through linking isotopes (e.g., α- or β- emitting isotopes) to targeting moieties (e.g., tumor specific small molecules, peptides, or biologics).3,4 The advent of commercially available antibody-directed radiotherapeutics began in 2002-2003 with the approval of Zevalin (ibritumomab tiuxetan; now marketed by Acrotech Biopharma) and Bexxar (tositumomab and iodine-131 [I-131] tositumomab; developed by GlaxoSmithKline) for the treatment of non-Hodgkin's lymphoma. Despite demonstrated efficacy and physician enthusiasm, sales of Zevalin and Bexxar remained low for over a decade post-launch, leading to multiple changes in ownership for Zevalin, and Bexxar's removal from the market.

First generation radiopharmaceuticals had several key challenges that contributed to limited commercial success. The production of radiopharmaceuticals often requires access to specialized facilities and equipment, as well as a reliable supply of radioisotopes. This limited availability can sometimes lead to challenges in meeting the demand for radiopharmaceuticals, particularly in regions distant from manufacturing and/or shipping sites or for specific isotopes such as actinium-225 and lutetium-177. Further, many radioisotopes used in radiopharmaceuticals have short half-lives, limiting the time available for their use, and resulting in the need for efficient delivery logistics or on-site production.5 The need for specialized facilities, equipment, and expertise required for their production and handling all contribute to their higher costs.

Second generation radiopharmaceuticals, Xofigo (radium-223 [Ra-223] dichloride; Bayer, approved in 2013), Lutathera (lutetium-177 [Lu-177] dotatate; Advanced Accelerator Applications, approved in 2018), and Pluvicto (Lu-177 vipivotide tetraxetan; Novartis, approved 2022), have been commercially successful. Pluvicto, which is composed of a human prostate-specific membrane antigen (PSMA) targeting ligand that is conjugated to the beta-emitting radioisotope Lu-177 for the treatment of metastatic castration-resistant prostate cancer, has been estimated to have annual sales as high as $1.3B.6 Improvements in efficacy over existing standards of care, evolving oncology practices to include radiation oncologists, and the use of radioisotopes with improved stability and safety have converged to reinvigorate the field. Though radiopharmaceuticals have shown great promise in the treatment of certain cancers, their therapeutic applications are currently limited to specific types of tumors; however, the development of effective radiopharmaceuticals for a broader range of diseases is an ongoing area of interest.

Increasingly the radiopharmaceutical use case extends beyond therapeutics and into the field of diagnostics. Diagnostic radiopharmaceuticals are specialized substances that contain a radioactive component and are used in medical imaging procedures to selectively accumulate in specific organs, tissues, or cells, allowing for the detection of abnormalities or functional changes. Such agents may be used for diagnosing tumors, neurological and neurodegenerative disorders, inflammation, and bacterial infections.[7] Diagnostic radiopharmaceuticals can detect/stage diseases, evaluate patients' eligibility for treatments (including radiotherapy), and monitor treatment effect. These typically contain a radioactive isotope that emits gamma rays or positrons (β+), allowing for imaging techniques such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT).[8] However, while radiopharmaceutical imaging techniques like PET and SPECT provide valuable functional and molecular information, they may have limitations in terms of spatial resolution and sensitivity compared to other imaging modalities like MRI or CT. This can impact the ability to detect small lesions or subtle changes in certain anatomical structures.

Theranostic radiopharmaceuticals represent an exciting and rapidly evolving field in medicine. Recently, there has been a significant push in the development

of theranostic radiopharmaceuticals, which combine both diagnostic and therapeutic properties creating a "see and treat" approach. Theranostic radiopharmaceuticals work in a two-step process. First, a diagnostic component is used to visualize and assess the disease or condition, following which the same or a complementary radiopharmaceutical is used for therapeutic purposes.

The advantage of theranostic radiopharmaceuticals lies in their ability to personalize treatment based on individual patient characteristics. By using the diagnostic component to assess the disease, clinicians can determine the presence, location, and extent of the target cells. This information helps in tailoring the therapeutic component to deliver precise and targeted radiation to the affected areas, minimizing damage to healthy tissues. Theranostic radiopharmaceuticals have shown significant promise in the field of oncology. Prior to Lutathera's ([Lu-177]Lu-DOTA-TATE) approval in 2018 for somatostatin receptor (SSTR) positive gastroenteropancreatic neuroendocrine tumors (NETs), NETSPOT ([Ga-68]Ga-DOTA-TATE) was approved in 2016 for detecting SSTR NETs. NETSPOT, which played a contributing role in Novartis's acquisition of Advanced Accelerator Applications, is currently used to detect, monitor progression, and determine appropriate candidates for Lutathera treatment. Diagnostic imaging is repeated after therapy where clinicians can assess the effectiveness of the treatment and make necessary adjustments if needed. The ability to combine diagnostics and therapy in a personalized manner holds great promise for improving patient outcomes, optimizing treatment strategies, and advancing precision medicine approaches.

Radiotherapies, theranostics, and radio-diagnostics are all commonly utilized within oncology indications. While approved radiotherapies and theranostics are currently limited to oncology, development efforts have recently begun to extend beyond oncology to include immunologic and neurological diseases. Whereas for radio-diagnostics, neurological diseases are a dominating field of interest, as they have been found to play a crucial role in the evaluation and diagnosis of conditions affecting the brain and nervous system, such as Alzheimer's disease (AD), Parkinson's disease, and migraine.[9] In neurology, radio-diagnostics provide valuable information about the structure, function, and metabolism of the brain, aiding in the identification and management of neurological disorders.[10] Currently, Amyvid (Eli Lilly, approved in 2012), a Florbetapir F 18 intravenous injection, is approved in the US for PET imaging of the brain to estimate the β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD). Radiopharmaceuticals labeled with specific ligands or tracers can target specific receptors or molecules in the brain, allowing for the visualization and quantification of these targets. This enables the assessment of neurotransmitter systems, receptor densities, and neurochemical processes, which can be used to identify patients at risk of developing a disease, monitor disease progression, or both, in a non-invasive manner.

Recent years have seen a flurry of activity surrounding radiopharmaceuticals. Growth in the field has been spurred by the improved specificity and efficacy of second-generation radiopharmaceuticals, improvements in

current supply-chain constraints, and emerging platforms that leverage the attributes of radionuclides as therapeutics and diagnostics, including their ability to penetrate safely and specifically act upon historically tough targets. These factors collectively contribute to the expansion and evolution of the radiopharmaceuticals industry, with a focus on improving patient outcomes and advancing precision medicine. Because of the rapid and exciting evolution of the field, we assessed the recent transactional (strategic and financing) landscape and public market dynamics.

Radiopharmaceuticals Transactional Landscape

Over the past 5 years there have been 91 strategic transactions in the radiopharmaceutical space, with the majority being for collaboration, co-development, and licensing-based agreements. Between 2018 and 2021, the transactional landscape has remained relatively stable, however between 2021 and 2022, there was a considerable increase in the number of deals struck, almost tripling in number (n=9, n=25, respectively; Figure 1).

Figure 1

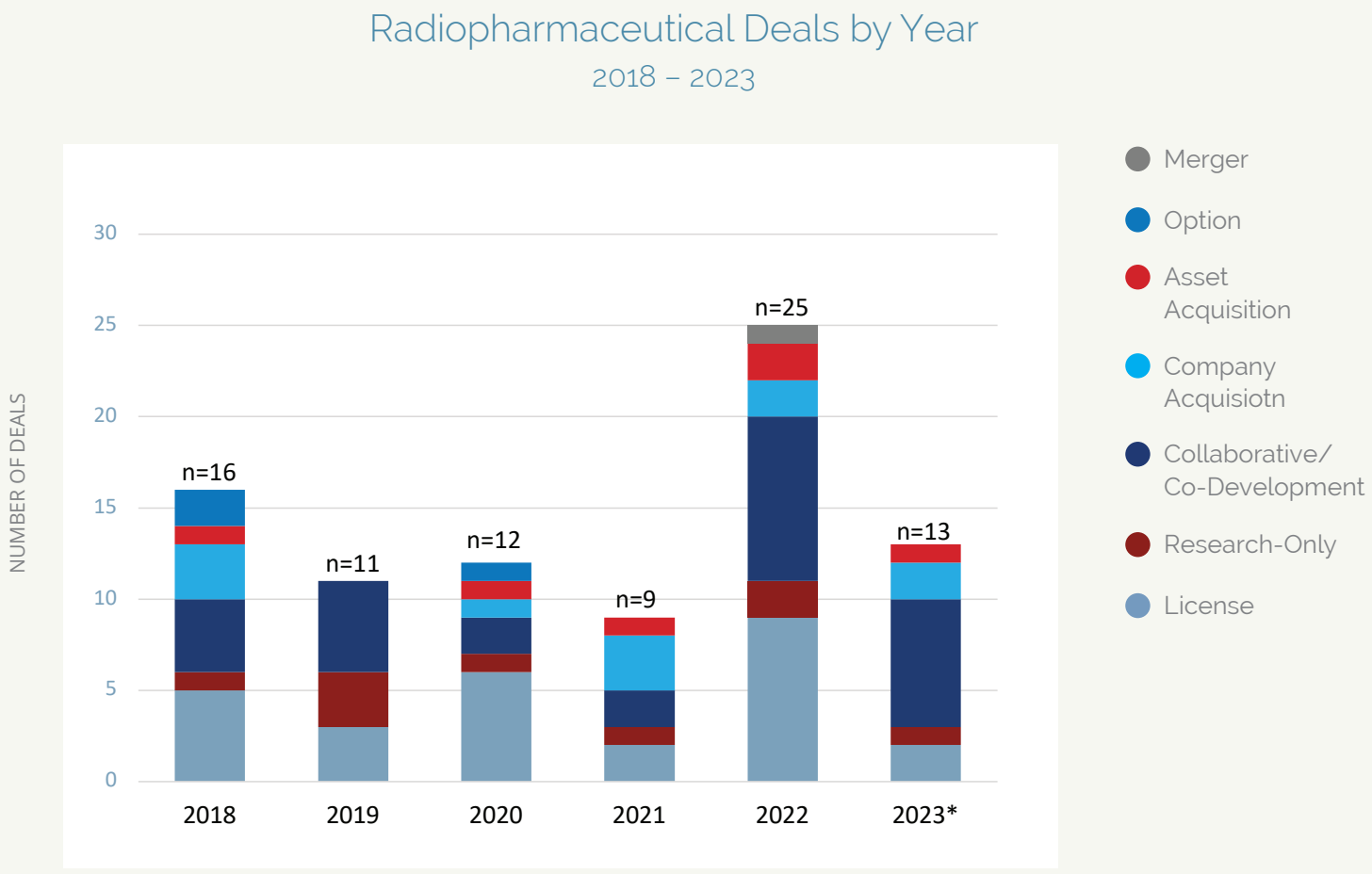
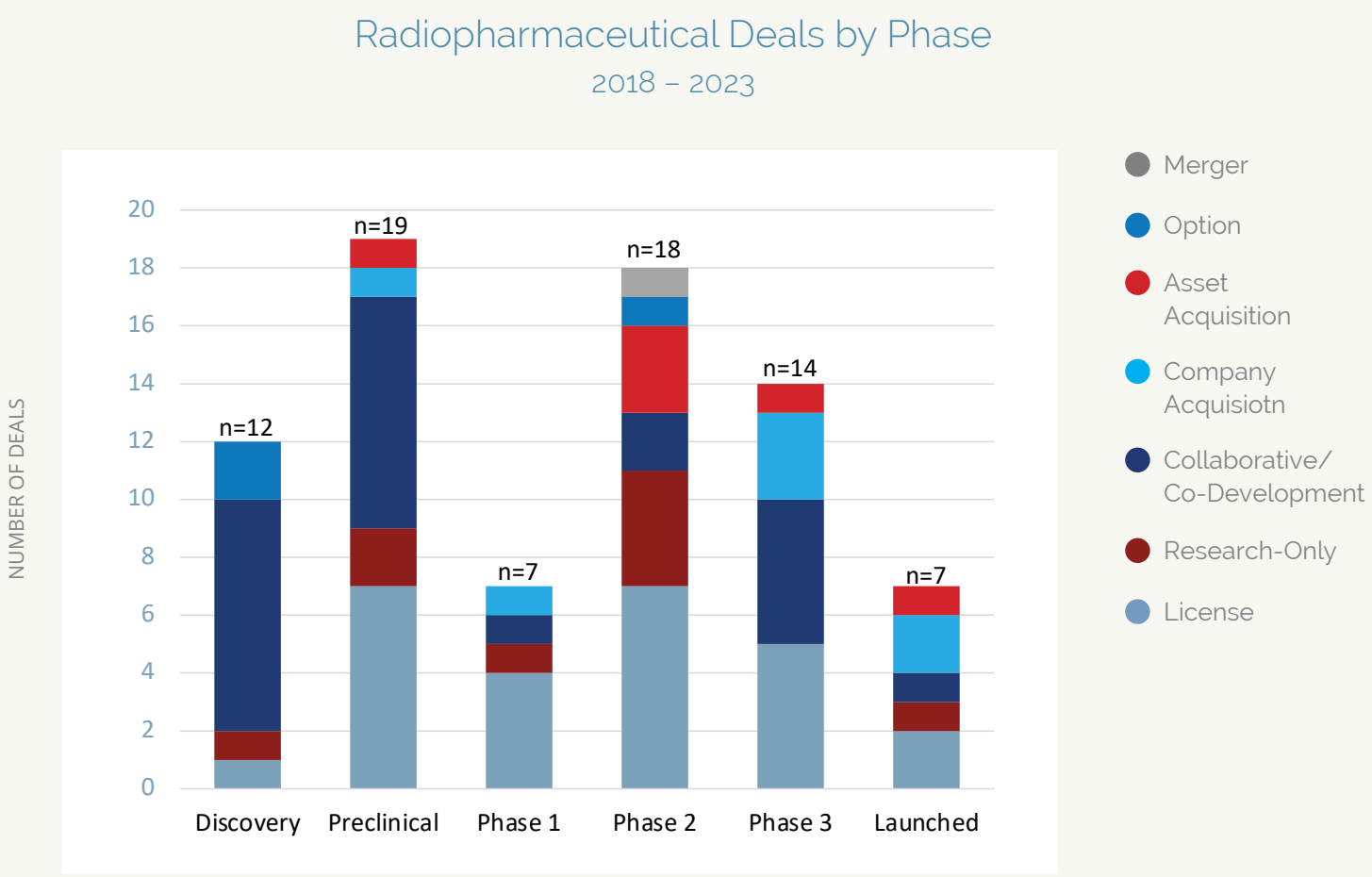


Figure 2



Notably, most deals have been struck for assets in the preclinical phase or in Phase 2 of clinical development (Figure 2). Preclinical deals have predominately been driven by firms with existing nuclear medicine capabilities (e.g., Fusion Pharmaceuticals, Novartis, and Viewpoint Molecular Targeting) and expertise seeking to expand their radiopharmaceutical pipeline with assets with robust preclinical data. Deals struck at Phase 2 have been predominately for licensing and acquisition deals of diagnostic radiopharmaceuticals to be used for identifying patients best suited for the partner companies' therapeutic asset(s).

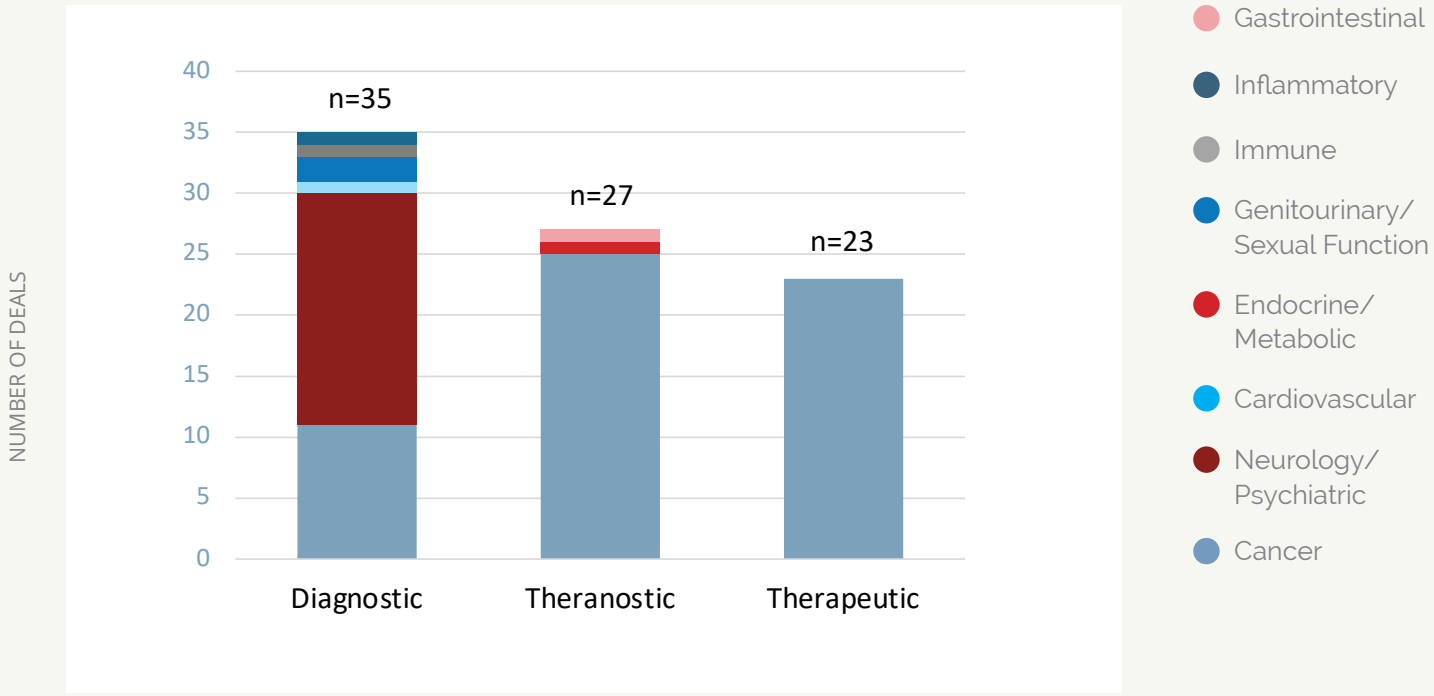
Diagnostic radiopharmaceuticals have commanded a considerable portion of the total number of deals in this space (~40%), followed by theranostic (~30%) and therapeutic radiopharmaceuticals (~30%; Figure 3). While cancer is dominating the deals in the theranostics and therapeutics space, neurology has commanded a substantial portion of the deals in the diagnostics space, alongside cancer.

Active consolidators in the space span global biopharma (e.g., Novartis, Bayer) to dedicated nuclear medicine firms (e.g., Fusion Pharmaceuticals,

Figure 3

Radiopharmaceutical Deals: Distribution by Modality

2018 – 2023



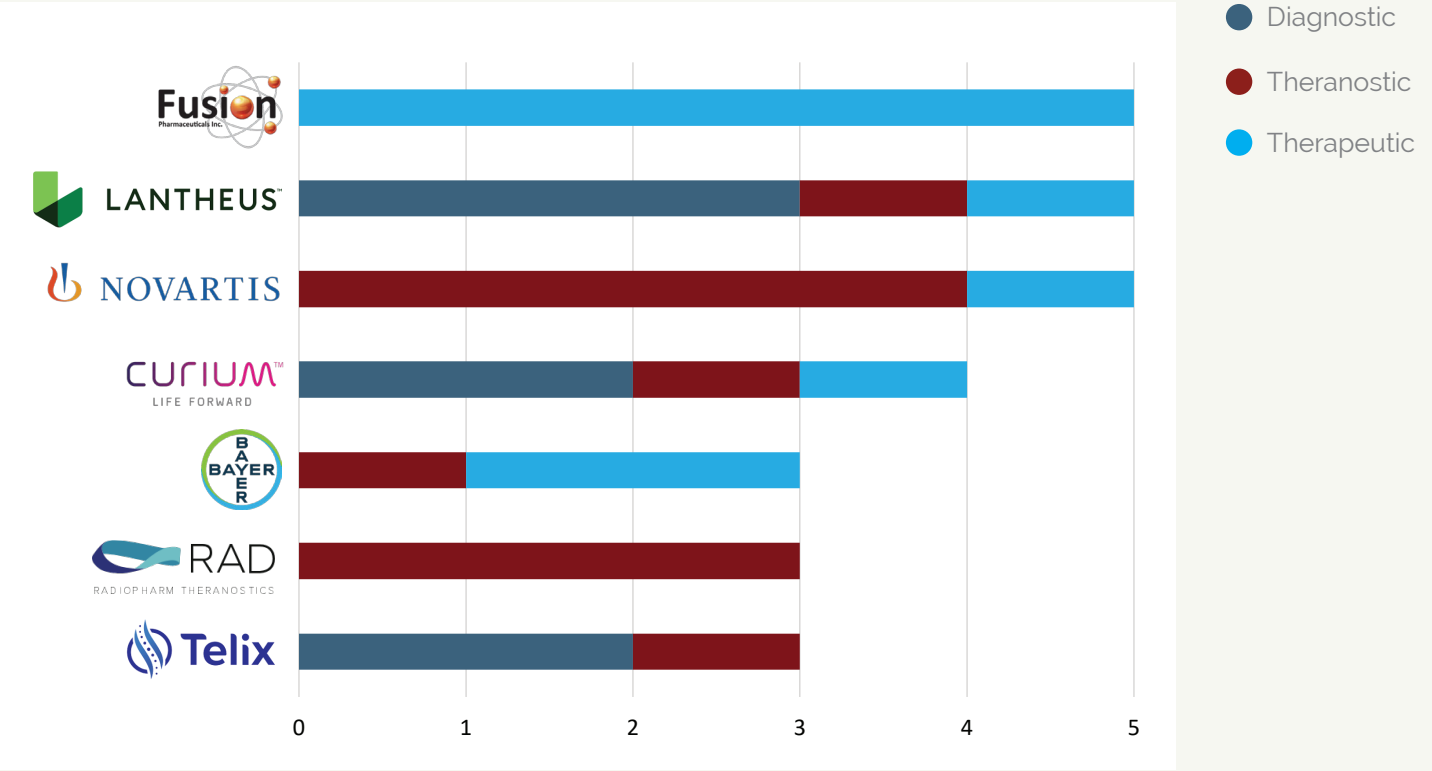
Curium Pharma), with deal activity spread across diagnostic, theranostic, and therapeutic modalities (Figure 4). Bayer, focused on developing therapeutic and theranostic cancer assets in the discovery and preclinical phases, penned a $1.745B deal in 2023, with Bicycle Therapeutics, paying out $45M upfront, to discover, develop, manufacture, and commercialize bicyclic radio conjugates using Bicycle's synthetic peptides for an undisclosed target in oncology. Bayer currently markets a radiotherapy Xofigo, approved in 2013 for prostate cancer treatment, and additionally picked up radiotherapeutics biotech Noria Therapeutics in 2021 along with its subsidiary PSMA Therapeutics. Since 2020, radiopharmaceuticals firm Fusion Pharmaceuticals has been rapidly expanding their pipeline of therapeutic-based assets for a variety of oncology indications, acquiring three separate pipeline assets and striking two individual collaboration/co-development deals.

Between 2018 and 2023, the average pre-launch deal value was $1,053M ($538M up-front, $515M milestone) across all stages of development and

Figure 4

Active Radiopharmaceutical Consolidators, ≥3 Deals

2018 – 2023



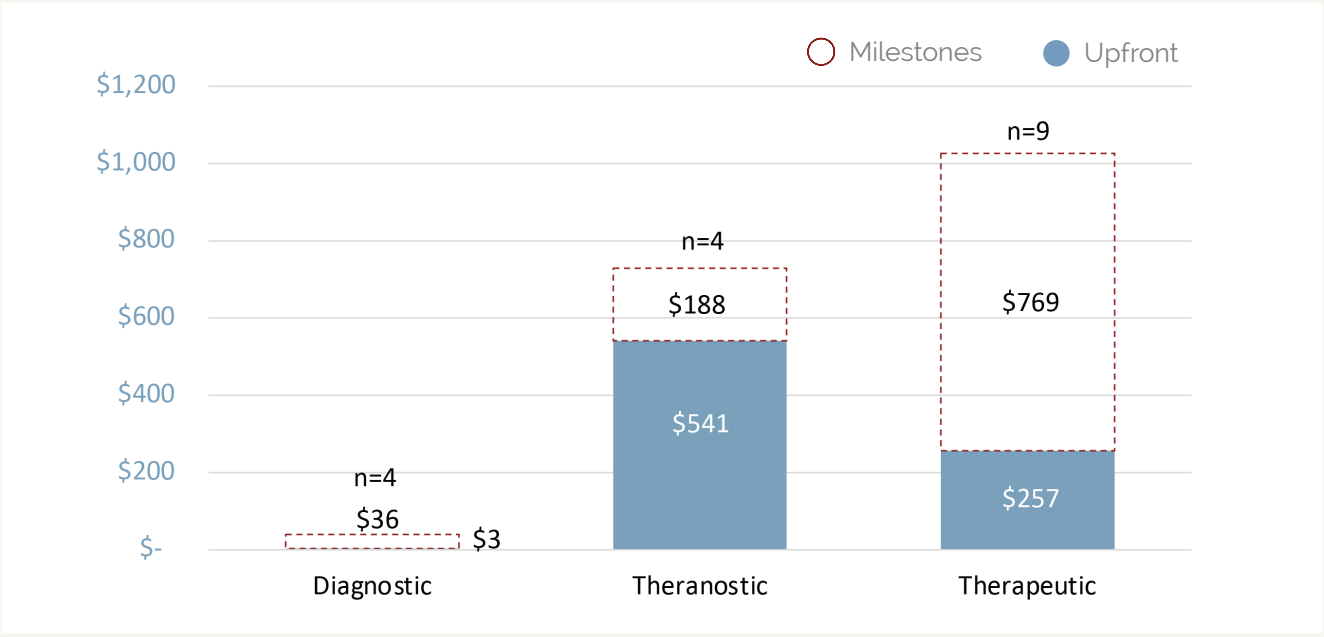
modalities (based on 19 disclosed deals; Figure 5). Compared to the average total deal value of diagnostic assets ($39M; n=4), the deal value for theranostic (n=4) and therapeutic (n=11) assets was considerably greater ($729M and $1,432M, respectively). The average up-front deal value for theranostic assets accounts for ~70% of the average total deal value, while that of therapeutic assets accounts for ~50% of the average total deal value. Theranostics presents a de-risked opportunity, given lower clinical and regulatory risk compared to therapeutic only assets, likely contributing to the greater upfront cost for these assets.

When considering deal value by maturity of asset, clinical stage assets command increasing value as the technology progresses through the clinic (Figure 6). Compared to early-stage clinical assets, discovery stage deals have commanded a high value. Deals struck at this phase were collaborations between global biotech firms (e.g., Novartis, Bayer, and Genentech) and

Figure 5 and Figure 6

Precommercial Radiopharmaceutical Deals: Value by Modality

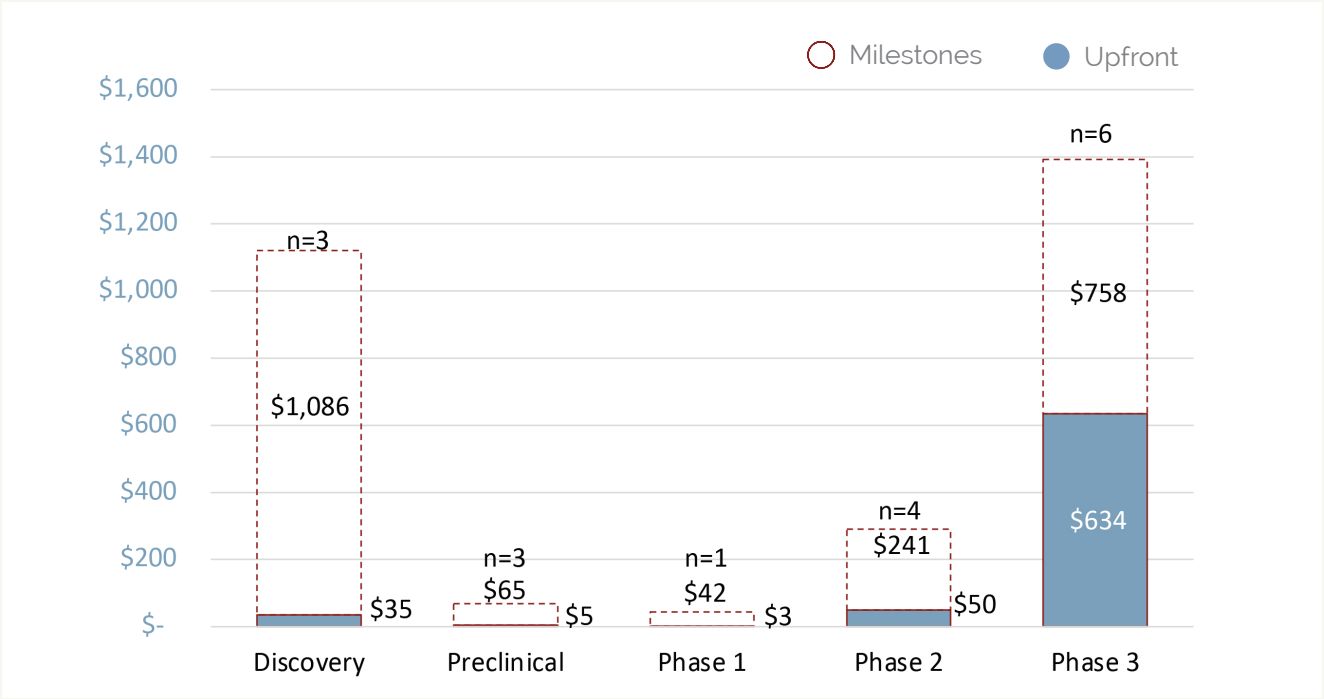
2018 – 2023



Sources: Cortellis

Precommercial Radiopharmaceuticals Deals: Value By Phase

2018 – Oct 2023



Sources: Cortellis

specialized nuclear medicine firms (e.g., Molecular Partners, Bicycle, PeptiDream) for the discovery, development, manufacturing, and commercialization of radiopharmaceutical therapies for oncology indications worldwide.

Whereas deals in the commercial stage have been primarily M&A-based deals with companies whose assets had been recently granted FDA approval, one such deal, with disclosed financials, came on the heels of the FDA approval of the NET diagnostic NETSPOT, and coincided with the FDA approval of the therapeutic Lutathera, a first-in-class Radioligand therapy that was approved in Europe at the time, in which Novartis penned a deal to acquire Advanced Accelerator Applications for $3.9B up-front in early 2018.

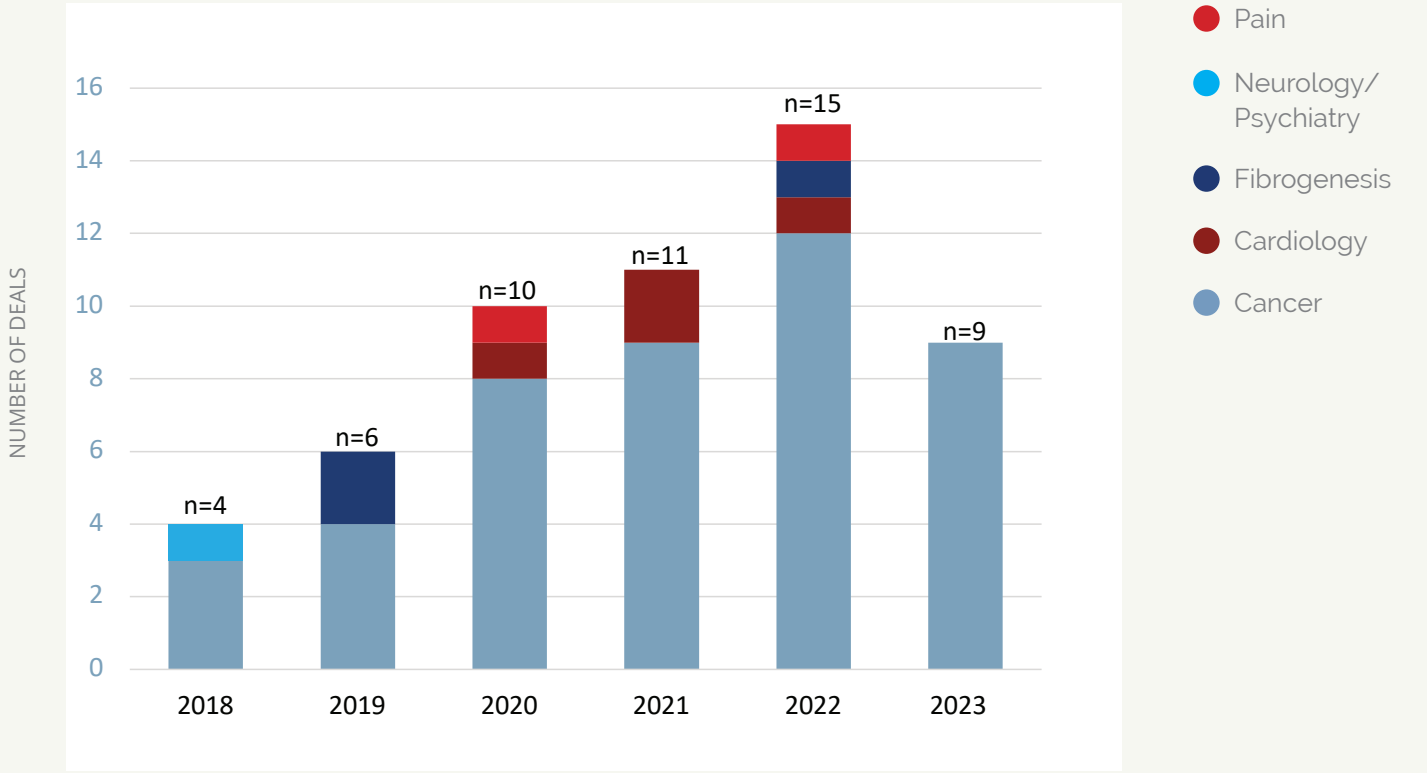
Financing

Since 2018, the number of financings occurring in the radiopharmaceuticals space has been steadily increasing (n=60), with predominant focus being on cancer indications (Figure 7). Theranostics represents the most active modality for financing (n=27), followed by therapeutics (n=24), and diagnostic (n=9)

Figure 7

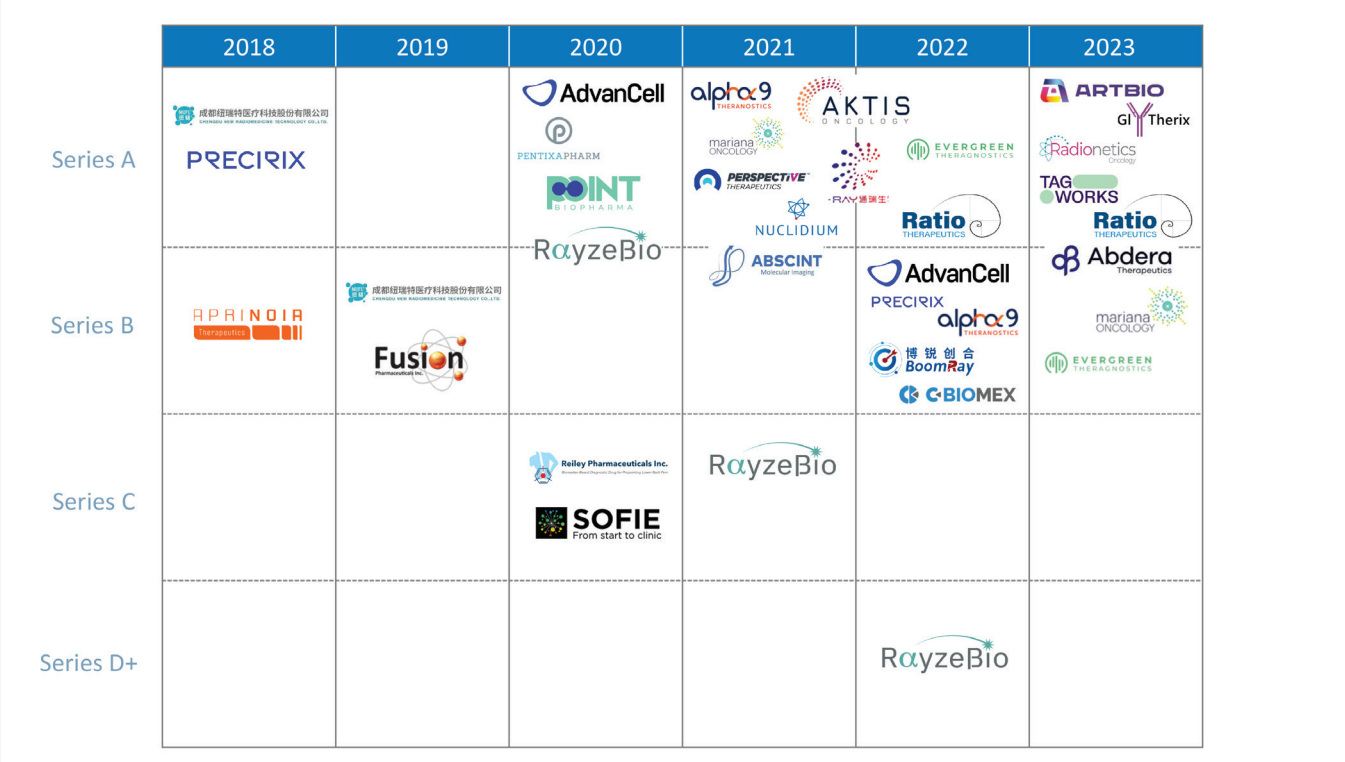
Radiopharmaceutical Financings by Year and Indication

2018 – 2023



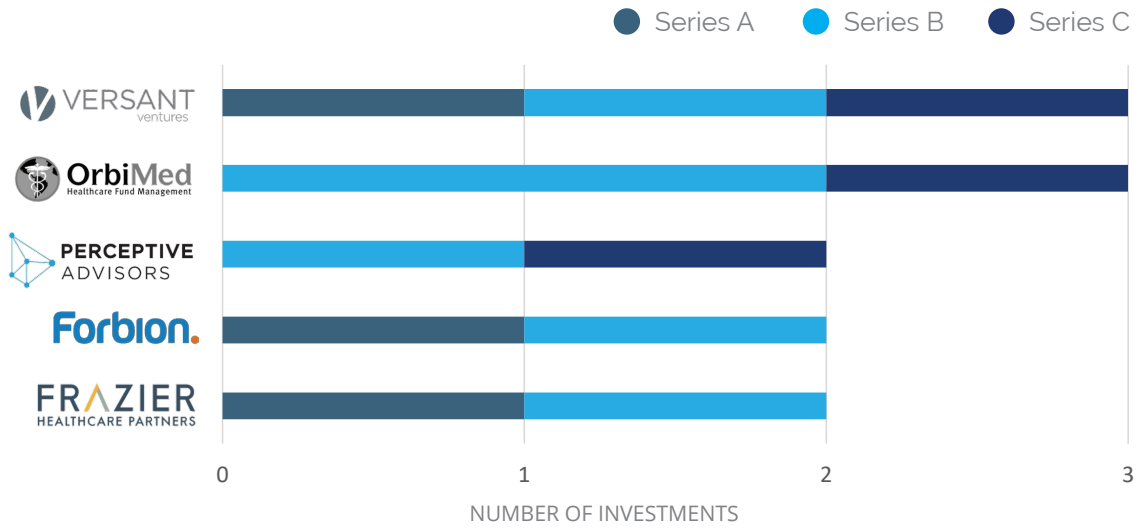
VC Financing Landscape for Emerging Radiopharmaceutical Technologies

2018 - 2023



Most Active VC/PE Firms in Radiopharmaceuticals

2018 – 2023

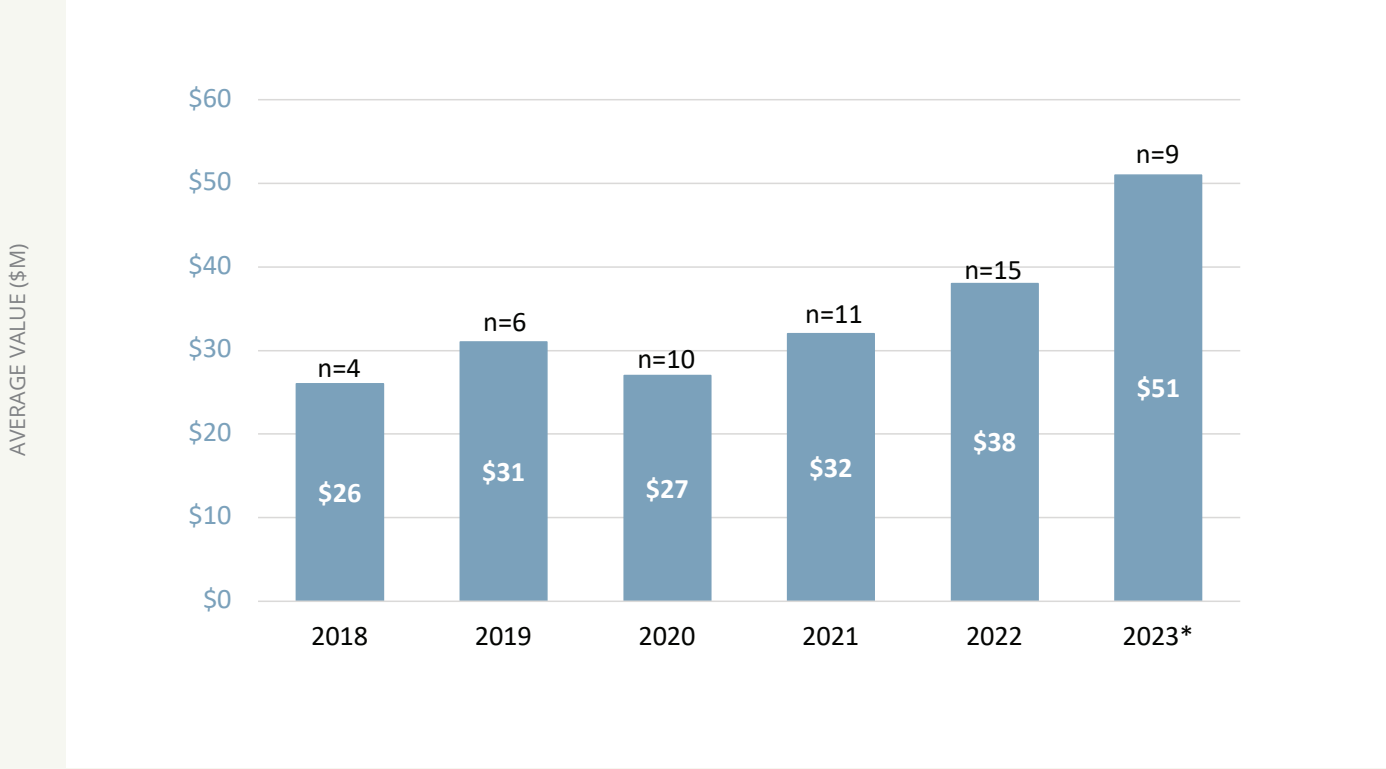


Sources: Pitchbook

Figure 10

Average Radiopharmaceutical Financing

2018 – 2023



assets, with the vast majority of financings occurring early at Series A (n=24) and B (n=15; Figure 8). From an investor perspective, private financing rounds in radiopharmaceuticals have come from a variety of life science investors, with only a few VC/PE firms consummating more than two deals in the space over the last 5 years (Figure 9). As interest and clinical development has been rising, so too has the level of financing, where the average financing across 14 raises in 2023 was $51M, ~2x greater than that of 2018 at $26M across 4 raises (Figure 10).

Radiopharmaceutical Public Companies Analysis

While the enthusiasm surrounding radiopharmaceuticals has led to an increase in dealmaking, the performance of radiopharmaceutical companies in the

Figure 11

2023 % Change in Performance for Radiopharmaceutical Companies Listed on Major American Stock Exchanges

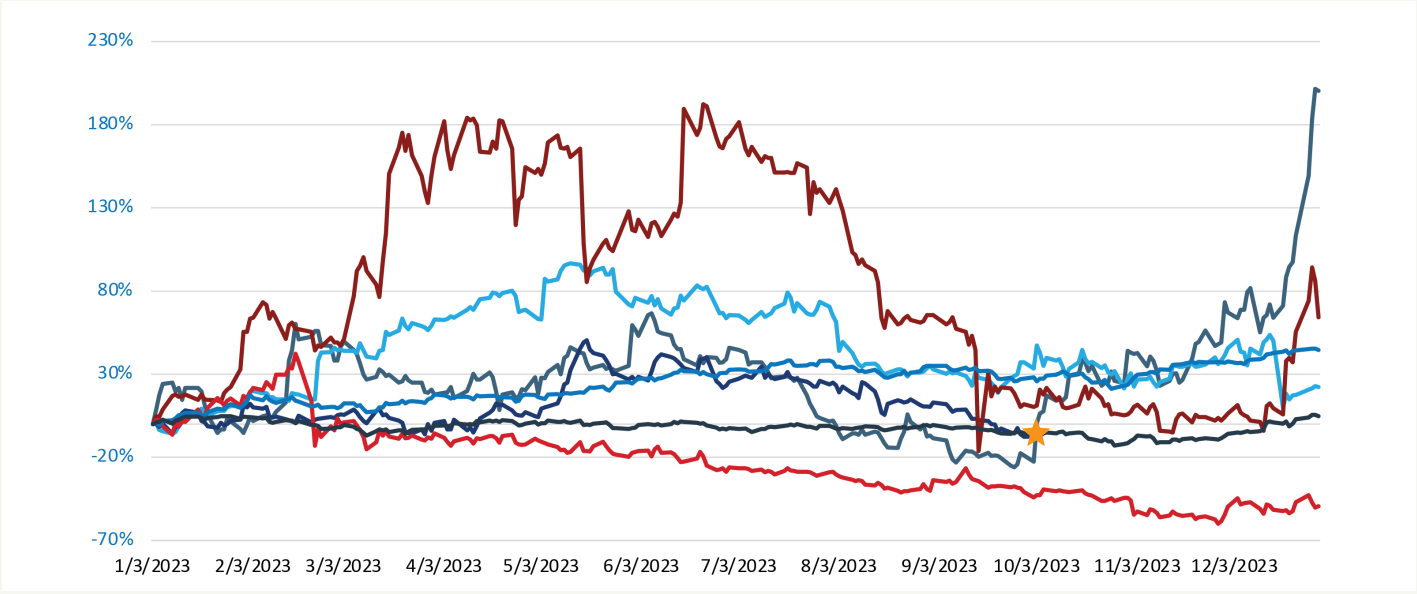


Table 1: 2023 % Change in Performance for Radiopharmaceutical Companies and Select Indices

	2023 Performance (%)
Fusion Pharmaceuticals	200%
Lantheus Medical Imaging	22%
POINT Biopharma	(7%)*
Perspective Therapeutics	64%
Actinium Pharmaceuticals	(49%)
MEDIAN	**22%**
AVERAGE	**46%**

	2023 Performance (%)
NASDAQ	45%
NASDAQ Biotechnology Index	5%

*2023 YTD Change in Performance of POINT Biopharma on October 2, 2023 (one day before

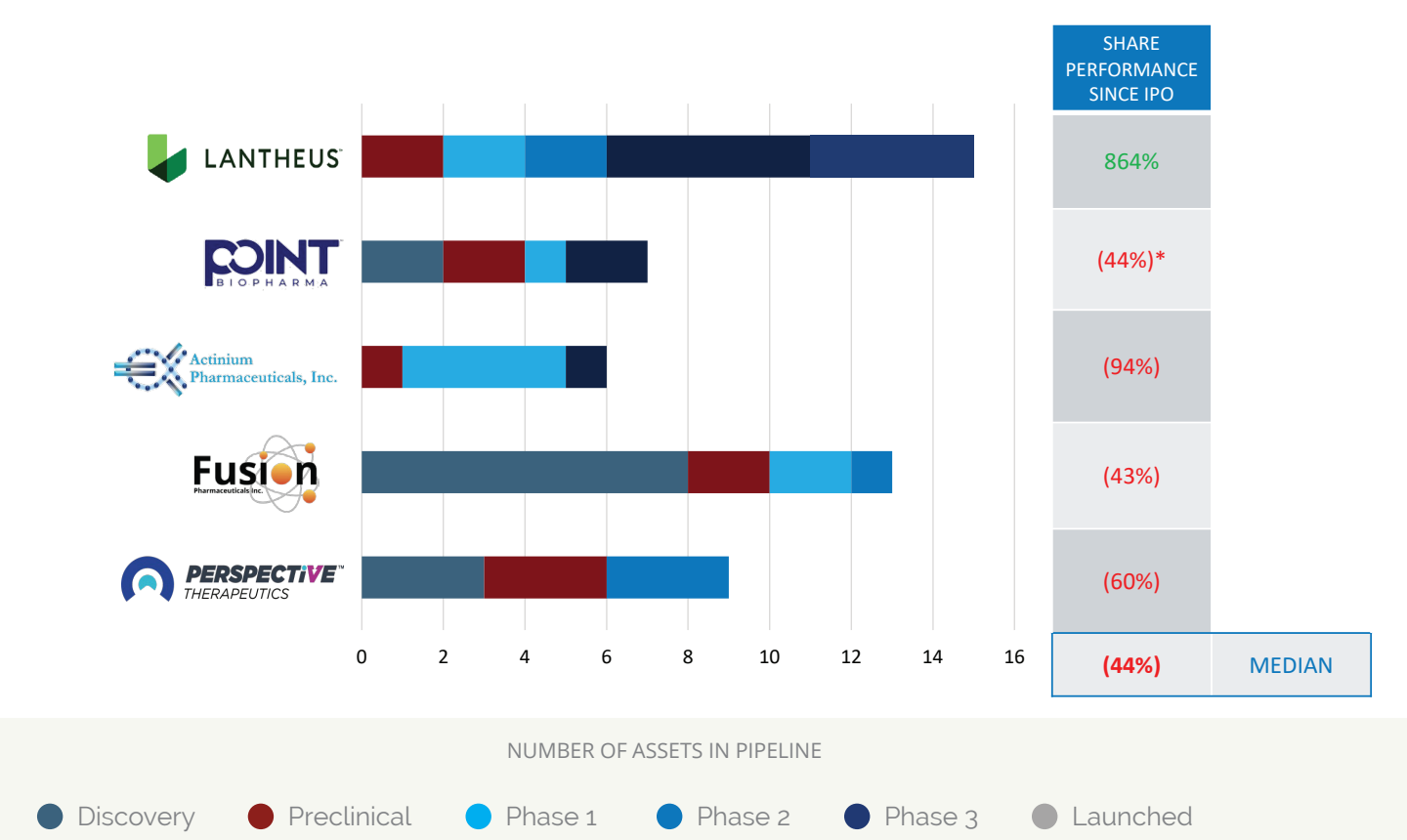
Sources: S&P Capital IQ

public markets has been mixed. As of the end of 2023, the median year-to-date performance of the 5 publicly traded radiopharmaceutical companies that have been listed on major US exchanges (NYSE or Nasdaq) since the beginning of the year was 22% (Figure 11), significantly stronger than the Nasdaq Biotechnology Index (NBI) which returned 5% in 2023 (Table 1). It's important to note that by the end of 2023, two public radiopharmaceutical companies had entered into agreements to be acquired. On December 26, 2023, RayzeBio entered into a definitive merger agreement with BMS to be acquired for $4.1 billion, reflecting a 134% premium of RayzeBio's share price at the time. Additionally, on December 27, 2023, Eli Lilly announced that they had closed their acquisition of POINT Biopharma for $1.4 billion, which was an 87% premium of POINT's closing share price a day before the acquisition was announced back on October 3, 2023. Large pharma's willingness to pay high premiums for radiopharmaceutical targets further demonstrates the burgeoning interest in the field.

One possible explanation for public radiopharmaceuticals outperforming the biopharma market in 2023 may be attributed to the buzz and excitement surrounding radiopharmaceuticals in the private markets, which has bled over into the public market. Reinforcing this theory was RayzeBio's (NASDAQ: RYZB)

Figure 12

% Change in Performance Since IPO for Radiopharmaceutical Companies



*Change in Performance since IPO of POINT Biopharma on October 2, 2023 (one day before the Eli Lilly's acquisition announcement)
Sources: S&P Capital IQ

IPO back in September prior to being acquired. RayzeBio, a vertically integrated radiopharmaceutical therapeutic company with its lead asset in Phase 3 of development for the treatment of gastroenteropancreatic neuroendocrine tumors, raised $358M when it went public on the Nasdaq on September 15th, 2023, giving them a valuation near $1B after their listing. Their $358M raise makes them the second largest biotech IPO of 2023, behind Acelyrin's (NASDAQ: SLRN) $540M. From an analysis of the gross proceeds and volume of life science IPOs this year, RayzeBio's IPO was found to be ~2.9x the average healthcare IPO size in 2023.

The median performance of public radiopharmaceutical companies year-to-date may appear promising, but the median performance since IPO tells a different story (Figure 12). Companies that have seen the greatest share price appreciation are those with commercial or late-stage clinical assets, while companies that have struggled have been those with early-stage assets. This is a common trend seen throughout biotech, as earlier-stage public biotech companies tend to be "boom or bust" due to their speculative nature and extended path to regulatory approval. As the IPO window begins to open in 2024, it is highly likely that public investors will focus their attention on more clinically advanced de-risked assets, and radiopharmaceuticals will be no exception.

Looking Ahead

With a significant amount of investment poured into early-stage companies, we expect pharma to continue their licensing and M&A activity as these novel technologies mature. As companies progress their programs through the clinic there are likely to be more potential partners for their technologies. With Eli Lilly's and BMS' acquisitions in late 2023, two additional global players have joined the likes of Novartis and Bayer as radiopharmaceutical players. Moreover, with the increasing emphasis on personalized medicine, theranostics are likely to continue to be of keen interest; indeed, theranostics commanded the greatest upfront value of modalities considered herein. The use of radiopharmaceuticals in areas beyond oncology is likely to bring additional strategics and VCs to the table. In fact, neurology was the leader when it came to diagnostic deals due to radiopharmaceuticals' unique ability of visualizing the brain and other parts of the central nervous system. Altogether, the radiopharmaceuticals space is charged with anticipation and high expectations as deals continue at pace.

Contact the authors or submit a question about Radiopharmaceutical development and funding: info@bblsa.com.

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