Radioligand Therapy: Seizing The Opportunity

Executive Summary

Radioligand therapies (RLTs) are an emerging class of targeted therapies that are part of a growing trend of "precision medicine" treatments. The RLT market is expected to grow significantly over the course of this decade, driven by several clinical and commercial factors, with increasing interest in this modality from the academic, clinical and investor communities. Although there are a number of compelling growth drivers for the RLT market overall, there are also several challenges that will need to be overcome if the market is to achieve its full potential. Integration of RLTs into broad clinical practice will require careful consideration of several factors including manufacturing and supply chain, settings of care and the patient journey, as well as commercialization challenges.

Key Takeaways

We estimate the market (excluding imaging agents) could grow from total sales of ~$750 M in 2022 to ~$5.5 B in 2028, a CAGR of ~40%

According to our analysis, there are currently 82 RLT assets in clinical development, spanning at least 10 solid tumor types and hematological malignancies, and involving 15 different isotopes. Combination approaches are an active area of focus

Given their higher potency and reduced off-target effects, there is increasing research and development interest involving alpha-emitting radioisotopes

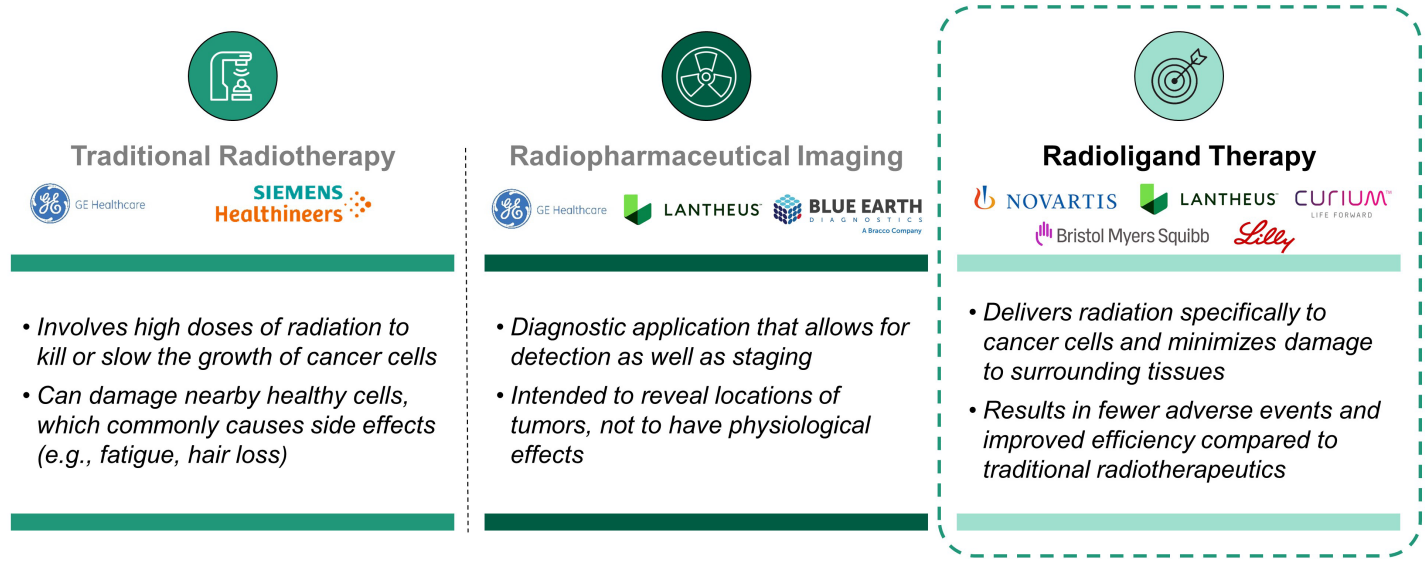
Developing and commercializing an RLT is different to a 'standard' pharmaceutical product, with a unique set of challenges that will need to be fully characterized and understood to successfully bring an RLT to market

For manufacturers aspiring to play a leading role in this market, it will also be important to understand what capabilities are required, when to invest, and at what level

Overview of Radioligand Therapies

Radioligand therapies (RLTs) are an emerging class of targeted therapies that are part of a growing trend of "precision medicine" treatments. RLTs are a component of a broader class of agents called radiopharmaceuticals, which can be used for diagnostic or treatment purposes. They target structural or biochemical variations on cancer cells to deliver highly potent forms of radiation specifically to these cells while minimizing damage to surrounding tissues, theoretically resulting in fewer adverse events and potentially improved efficiency compared to traditional radiotherapeutics. Importantly, these therapies also have associated radioligand imaging properties that use the same structural variation on cells to allow physicians to image the patient and assess targeting of the agent prior to treatment initiation, an advantage over existing therapeutic approaches as it allows physicians to see whether the treatment is likely to work.

FIGURE 1 – Key Radiation Medicine Market Segments



RLT Structure

RLTs are made of three key components – a cancer-targeting ligand, a radioisotope, and a linker to connect them. There are a variety of targeting ligands that specifically bind to a cancer cell, though the most common are antibodies, peptides, and small molecules that recognize cell surface markers or biochemical characteristics that are either preferentially expressed or overexpressed on cancer cells. Binding of the ligand to the cell surface brings the linked radioisotope into closer proximity of the cancer cell, leading to DNA damage and ultimately cell death. The decay caused by binding to a cancer cell releases energy that can also damage the DNA of nearby cells, potentiating a 'bystander effect.' Radioisotopes used in RLTs may emit either alpha- or beta- particles, with each having distinct properties and potential use cases. Alpha emitting-isotopes emit high-energy alpha particles when they decay that are large and heavy, causing them to lose their energy over shorter distances; beta-emitting isotopes emit beta particles that penetrate deeper than alpha particles, though cause less clinically relevant damage to DNA. The shorter penetration of alpha particles is thought to potentially reduce safety and side effect concerns relative to beta particles as alpha particles likely have reduced 'bystander effects' on non-cancer cells. Given their higher potency and reduced off-target effects, there is increasing research and development interest associated with the use of alpha-emitting radioisotopes (specifically Actinium and Lead), however manufacturing and procurement constraints, compounded by healthcare provider experience of working with beta emitters, mean that currently approved RLTs use beta emitting radioisotopes.

Table 1 – Isotopes in Pre-clinical and Clinical Development

Isotope	*Emitter Type*	*Half-life*
Actinium-225	Alpha	10 days
Astatine-211	Alpha	7.2 h
Copper-67	Beta	2.6 days
Indium-111	Alpha	2.8 days
Iodine-124	Beta	4.2 days
Iodine-131	Beta	8 days
Lead-212	Alpha	0.4 days
Lutetium-177	Beta	6.6 days
Rhenium-186	Beta	3.8 days
Rhenium-188	Beta	16.9 hours
Samarium-153	Beta	1.9 days
Terbium-161	Beta	6.9 days
Thorium-277	Alpha	18.7 days
Tin-117	Gamma	13.6 days
Yttrium-90	Beta	2.7 days

A Brief History

Delivering radiation directly to cells is not a new approach. Radiotherapy was first used over 100 years ago to treat cancer (approximately 50% of cancer patients still receive external beam radiation therapy at some point during their treatment today), while radioactive iodine has been used to treat thyroid cancer since the 1940s. The first RLTs to be licensed by the FDA did not see widespread adoption for a variety of reasons, however, the field really started to grow following the approval of Pluvicto in March 2022, for the treatment of men with PSMA-positive metastatic castrate resistant prostate cancer (mCRPC) following treatment with androgen receptor pathway inhibitors and taxane-based chemotherapy. Pluvicto is the first approved RLT to target a broad patient population and has seen strong commercial success despite initial supply chain issues that led to treatment delays, providing commercial proof of concept for RLTs as a mainstream treatment approach. Development is currently ongoing that will likely see Pluvicto used in a broader patient population in earlier treatment lines.

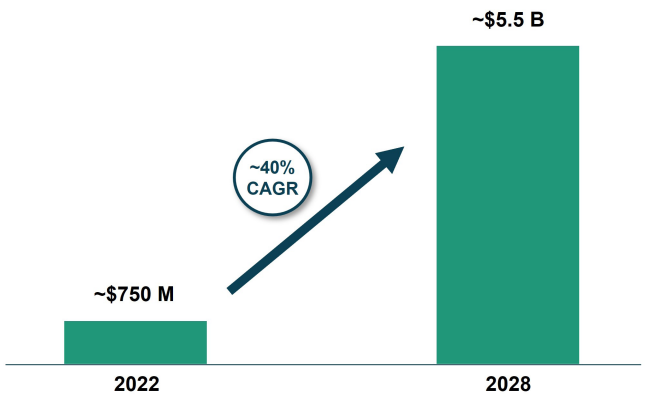
Growth of the RLT Market

The RLT market is expected to grow significantly over the course of this decade, driven by several clinical and commercial factors:

- The ability to image and quantitatively characterize the likely biological outcome of the RLT in addition to potentiating a treatment effect.
- Increased availability and lower cost of radioisotopes (particularly alpha emitters).
- Increasing confidence in RLT as a safe and effective approach to treat a broad range of solid tumors.
- Longer-term safety and efficacy data reinforcing the clinical utility of RLTs in indications with large patient populations.
- Growing pre-clinical and clinical interest and focus on combination approaches with treatment modalities that are complementary to RLT, driven by the potential for improved outcomes with limited incremental toxicity

Given the current pipeline, we estimate the market (excluding imaging agents) could grow from total sales of ~$750 M in 2022 to ~$5.5 B in 2028, a CAGR of ~40%.

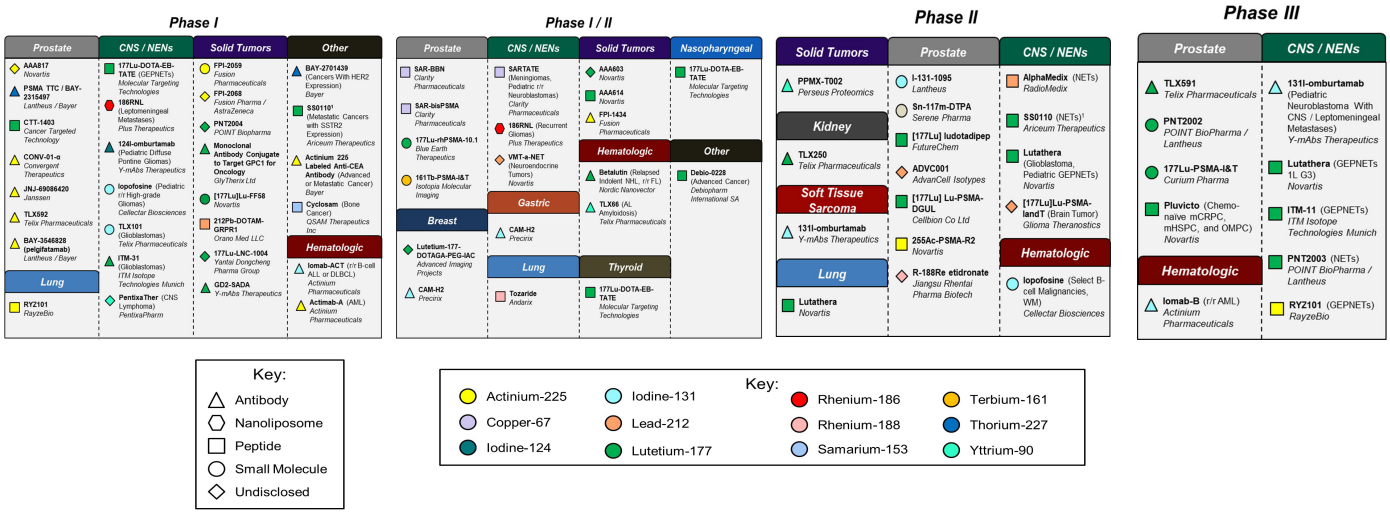
FIGURE 2 – RLT Market Growth



Current RLT development spans a wide range of tumor types (several of which have large eligible patient populations such as breast, lung, and hematologic cancers) and involves fifteen different isotopes. As well as significant single agent development, combination therapy with RLTs is also being investigated, as induction of additional DNA damage and biochemical cell signaling cascades through combination with other modalities such

as chemotherapy and immune-oncology (IO) therapies is postulated to yield greater therapeutic effect. Early-stage research has indicated a synergistic cell killing effect with PD-L1 inhibitors when used in combination with RLTs, while DNA Damage Response (DDR) Inhibitors such as PARP inhibitors that interfere with the repair of DNA breaks and leave the cell with significant DNA damage may compound the cell killing effects of RLTs. There are also ongoing combination trials of RLTs with other classes of agents that lead to tumor cell killing, such as CDK4/6 inhibitors, mTOR inhibitors, and DNA methyltransferase inhibitors among others.

FIGURE 3 – RLT Clinical Development Landscape



Note. Excludes RLT development from academic or cancer centres

As a result of the expected market growth, there has been significant deal flow into the RLT space over the last couple of years. A recent report from Fierce Biotech noted an approximately 550% increase in venture capital deals in 2023, worth over $400 million, up from approximately $65 million in 2017. New industry entrants include both established large pharmaceutical manufacturers and smaller specialized biotechnology companies. According to our analysis of the RLT pipeline, there were over 60 players in the RLT field at the end of 2022, and this is only likely to increase with the advent of greater clinical and commercial success with these therapies.

FIGURE 4 – Recent RLT Deals

Key Considerations for Manufacturers

Although there are a number of compelling growth drivers for the RLT market overall, there are also several challenges that will need to be overcome if the market is to achieve its full potential. Any manufacturer seeking to enter and successfully compete in the RLT space must have a thorough understanding of the key differences between RLT and traditional therapies. As RLT development requires expertise in a broad range of disciplines including radiochemistry, pharmacology, medical physics, radionuclide imaging and dosimetry (several of which will be new territory for most manufacturers), having the right technical and functional capabilities and an organizational mindset that is familiar with the unique challenges of RLT development and commercialization will also be critical success factors.

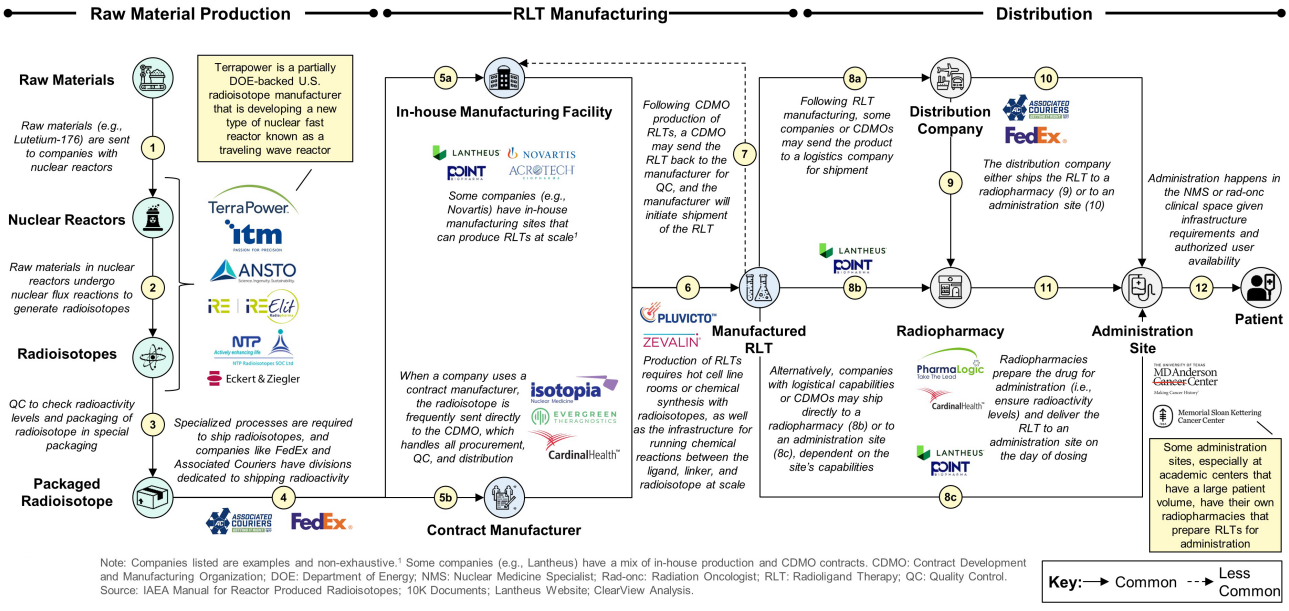
Manufacturing and Supply Chain

RLT production requires a complex supply chain of isotope production, RLT generation, and shipment to administration sites. Manufacturing and distribution are key steps in the RLT 'product journey', with significant complications unique to the field, many of which relate to the short half-life of radioisotopes. An RLT with a short shelf-life will require 'just-in-time' manufacturing processes, ideally in a decentralized fashion close to where that RLT will be used. Centers that use RLTs and radio-imaging tools at a high-volume such as academic medical centres may have their own internal radio-pharmacies to prepare the RLT for end-point administration, while centralized radio-pharmacies may fill this role for centers that do not have these capabilities by receiving and labelling 'cold' RLTs before distribution to the administration site.

A manufacturer of RLTs may produce the RLT 'in-house' or use a Contract Development and Manufacturing Organization (CDMO). Similar to the cell therapy space when it was more nascent, there are still relatively few CDMOs dedicated to RLT production (e.g., CardinalHealth and SpectronRx), though this is expected to grow over time. Larger companies with more resources or companies more heavily invested in RLTs typically invest in their own facilities, while smaller companies or those with earlier-stage assets may favor the use of CDMOs to streamline production. Selection and appropriate use of CDMOs should not be undertaken without conducting proper diligence including the CDMO's existing relationships with radioisotope producers and radio-pharmacies.

Manufacturers seeking to enter the RLT space must extensively map the product journey from raw materials to radiolabeled therapy to understand all 'pain points' along the way, assess the tradeoffs of investing in in-house manufacturing capabilities or engaging with CDMOs, and establish frameworks for evaluating potential CDMO partners.

FIGURE 5 – Steps in the RLT Production Process



Note: Companies listed are examples and non-exhaustive.[1] Some companies (e.g., Lantheus) have a mix of in-house production and CDMO contracts. CDMO: Contract Development and Manufacturing Organization; DOE: Department of Energy; NMS: Nuclear Medicine Specialist; Rad-onc: Radiation Oncologist; RLT: Radioligand Therapy; QC: Quality Control.
Source: IAEA Manual for Reactor Produced Radioisotopes; 10K Documents; Lantheus Website; ClearView Analysis.

Settings of Care and the Patient Journey

Currently, RLTs are typically administered in academic centers or RLT 'Centers of Excellence' due to the availability of the required personnel and specialist infrastructure, as well as certification and training requirements. Many of these sites have prior experience with nuclear imaging tools for diagnostic purposes and the necessary licenses to work with specific radioisotopes, thereby accelerating the development of protocols for novel radiopharmaceuticals intended for therapeutic use. Institutions are responsible for amending their radioactive material (RAM) license to accommodate new RLTs and higher volumes of radioactivity, while authorized users and other personnel responsible for handling and administration of RLTs must obtain individual certification from recognized accrediting bodies. As the use of RLT increases, it will be important to understand how these infrastructure requirements may limit adoption of RLTs for larger patient populations.

Coordination between the manufacturing site, radio-pharmacy, and hospital is critical. For RLTs with short half-lives, the product must reach patients within hours of production to limit the impact of radioactive decay on the efficacy of the therapy. Therefore, unlike traditional therapies, RLTs cannot be produced in large quantities and stored indefinitely at the administration site and are generally produced on an "as-needed" basis for each individual patient. Following successful administration of the RLT, the administration site must then coordinate proper waste management to ensure that the radioactive compounds are properly disposed of.

The RLT patient journey is also more complex than for a non-RLT product. Multiple stakeholders from different functional and specialist areas are involved in the prescription, handling & administration of RLTs, requiring a coordinated, multi-disciplinary approach involving members of the medical oncology and nuclear medicine teams before, during, and after administration. Patients must receive additional consultation and radiation education prior to administration, and in most cases prior to scheduling and ordering. There are also strict monitoring protocols in place following administration that must be adhered to. For many patients, there is an inherent concern about being treated with radioactive material and exposure to lingering radiation that is actively decaying in the patient post RLT administration, so proper counselling and education is necessary.

For new manufacturers in the RLT space, it is therefore critical to comprehensively assess administration sites to ensure the successful handling, administration and disposal of the product. It will also be essential to holistically map how patients flow through the various stages of their treatment journey (including diagnosis, referral, administration and monitoring) to ensure the safe and effective delivery of care.

FIGURE 6 – The Multi-disciplinary Nature of RLT

Illustrative RLT Stakeholder Map *(Oncology)*

	Prior to treatment		Day of treatment			Following treatment
	Treatment Decision	Consultation	Preparation	Administration	Monitoring & Discharge	Follow-up
Nuclear Medicine Physician	✓	✓		✓	✓	✓
Medical Oncologist	✓	✓				✓
Radiologist	✓					
NM Technologist			✓	✓		
Nurse		✓	✓	✓	✓	✓
Radiopharmacist			✓			

Nuclear Medicine Physician

- Work closely with med-oncs. to determine the role of RLTs in the treatment paradigm
- Responsible for ordering & administering RLTs; limited involvement in overall tx management
- Some level of involvement in management of RLT-related adverse events

Medical Oncologist

- Primary managers, follow patients throughout the treatment process
- Manage tx-related side-effects and therapy change-related decisions
- Manage co-administration of chemo, ADTs etc. with RLT

Radiopharmacist

- Specialize in preparing and handling of RLTs for use by NMS / radiation oncologists
- Fill prescriptions orders and receive RLTs from manufacturers
- Limited / no involvement in the RLT administration and patient monitoring

Commercialization of RLTs

An RLT-specific go-to-market strategy must consider a broader range of stakeholders in addition to medical oncologists, including radio-pharmacists, nuclear medicine physicians, and radiation safety personnel, many of whom will not be part of standard manufacturer outreach. While the commercialization process for RLTs for patients with PSMA-positive mCRPC is becoming increasingly well understood, gaining an understanding of the steps in the process for tumor types where RLT is not established will be important to determine how RLTs can be effectively integrated into clinical care for patients with these histologies, and consequently provide a basis for commercialization approaches.

RLT players will also need to understand the referral patterns of patients from the community into established RLT centers, especially as the use of RLTs extends to additional tumor types, as well as the treatment decision-making behaviors of the referring physician, to determine barriers to getting patients to the proper sites of administration. While many RLTs will be targeting tumor types with large, well-defined patient populations, referral network mapping can be complicated if the RLT is targeting a rare tumor type with a poorly identified patient population, though this can be alleviated through advanced analytics-driven predictive modeling that can identify potential patients and / or healthcare providers and sites that likely treat these patients. This foundational work is crucial for a manufacturer to efficiently plan field force structure and engagement of referring physicians.

For manufacturers who can commercialize their own assets, a traditional sales-led approach will not be appropriate given the multi-disciplinary nature of RLT administration. Commercialization of RLTs requires significantly more interactions for effective marketing over traditional pharmaceuticals, potentially coordinated via a Key Account Manager with specialized knowledge of the radiopharmaceutical space and who can coordinate relevant internal and external stakeholders effectively. Another consideration related to the unique challenges in the handling and administration of RLTs is the need for additional education for patients as well as other HCPs such as nurses who may be less familiar with the side effect profile of RLTs.

For smaller companies without internal commercialization capabilities, selection of the right commercial partner will be key and should consider factors such as the partner's experience of working with novel modalities, whether they have assets that may be combinable with their own, existing relationships in the same tumor type, and their history of collaboration.

The unique nature of RLTs necessitates a more nuanced commercialization strategy relative to traditional therapies. Due consideration should be given to how to engage non-traditional stakeholders, and also how operational hurdles and challenges may impact the willingness to use RLTs in new tumor types. Crafting an effective go-to-market strategy should take account of referral challenges, and also the appropriate customer-facing team size and structure.

Conclusion: A Strategic Plan For Success

Despite several barriers, the use of RLTs will likely become an increasingly important part of the treatment armamentarium for many solid and hematologic tumors moving forward due to their targeted nature, efficacy and side effect profile. There are multiple operational hurdles to be aware of along the value chain, so navigating the complexities of RLT treatment and implementing workable solutions will be critical to enter this space and compete successfully. For manufacturers aspiring to play a leading role in the RLT market, it will also be important to understand what capabilities are required, when to invest, and at what level.

About ClearView Healthcare Partners

Founded in 2007, ClearView Healthcare Partners is a global strategy consulting firm serving the life sciences sector, with offices in Boston, New York, San Francisco, London, and Zurich ready to support clients in complex engagements with local expertise.

ClearView combines international industry knowledge and deep scientific expertise in every major therapeutic area and across modalities with an extensive network of external stakeholders to deliver practical and actionable recommendations. ClearView's projects include cross-functional support at the corporate, franchise, and product levels for pharmaceutical, biotech, medtech and digital, and diagnostics companies, along with investment support across all phases of the transaction cycle for private equity and institutional investors.

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