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The Advent of Radioligand Therapies: A 2024 Snapshot on Prostate Cancer

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Introduction

In oncology, several biotech and pharma companies have investigated therapeutic modalities over the last few years, with the advent of immuno-oncology treatments, antibody drug conjugates, and targeted therapies. Among the modalities deployed by companies attempting to unlock the true potential of personalized medicine, radioligand therapies (RLT) are an increasingly appealing option. Over the last 12 months, a spending spree of acquisitions demonstrated the interest of major pharma players, including AstraZeneca, Bristol Myers Squibb, and Eli Lilly, in the RLT space, although these companies are modality-naïve. These large acquisitions likely found encouragement in the successes of Novartis' Lutathera®, launched in 2018 and Pluvicto®, launched in 2022, the latter targeting metastatic prostate cancer (mPCa) patients. Most RLT pure players are currently investigating this therapeutic area where the modality shows positive results.

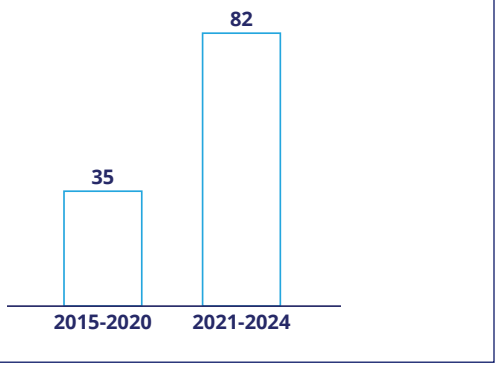
This paper provides an overview of the advent of RLTs through the example of mPCa, highlighting clinical and development trends along with selected strategic considerations in key markets.

The Number of RLT Candidates Targeting mPCa Increases

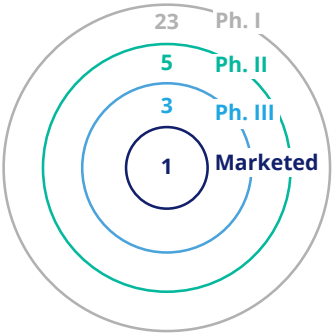
In 2023, the number of mPCa incident cases in the United States (US), France, Germany, Italy, Spain (EU4), and the United Kingdom (UK) combined reached more than 500,000, with ongoing growth of over 1% per year.[1] Significant unmet needs remain for better management and treatment of patients with mPCa. Those include the limited effectiveness of treatment options, especially when patients become castrate-resistant; the absence of optimal treatment sequence; and the relative lack to date of biomarkers for effective targeted therapies as compared to other cancers. As a result, mPCa is estimated to cost between $5 billion and $8 billion to the healthcare system in the US alone.[2]

RLTs have become a credible therapeutic option for mPCa and drive an increasing number of clinical development programs. Indeed, while 35 mPCa RLT-related clinical trials were initiated between 2015 and 2020 in selected geographies,[3] this number increased to over 80 between 2021 and 2024. In fact, more than 25 clinical trials began in the first six months of 2024 alone. As of July 2024, more than 30 different RLTs were under investigation in mPCa, including three in Phase III whose developers expect regulatory approval within the next 12 months.

Total number of RLT clinical trials initiated in the US, Europe, Japan, Australia, and South Korea between 2015 and H1 2024



mPCa RLT competitive landscape as of H1 2024: total number of products by latest development phase in the US, Europe, Japan, Australia, and South Korea

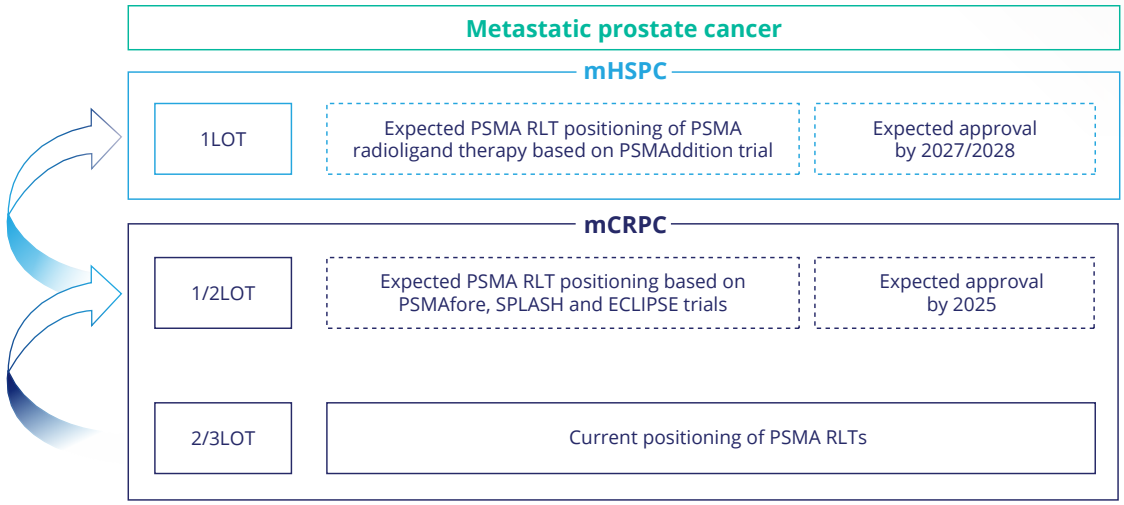


Note: [1]Alira Health analysis. [2]Olsen TA et al. (2022), The Cost of Metastatic Prostate Cancer in the United States – Urology Practice; [3]US, Europe, Japan, Australia, and South Korea.

A Favorable Clinical Environment Leading to a Strong RLT Uptake

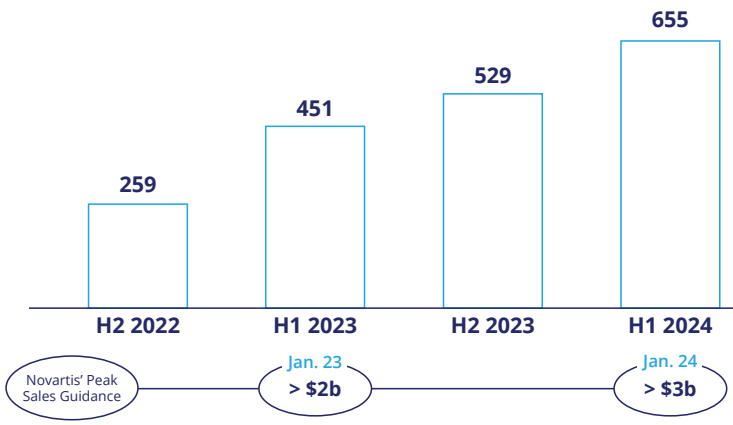
The number of new RLT candidates in mPCa demonstrates the growing interest from biopharma companies in this therapeutic area, with recent clinical developments making the mPCa environment even more favorable. Pluvicto started in 2022 with a second/third line of therapy (LoT) positioning in the metastatic setting. However, there are currently several Phase III trials investigating an earlier use of RLTs in 1/2LoT pre-chemotherapy treatment.[4] Novartis' PSMAddition trial aims to generate evidence for Pluvicto's use in 1LoT, in combination with hormonal treatments, expanding its label. Should Novartis succeed with this positioning, the ability to treat patients earlier in their disease progression would significantly expand the addressable patient pool for RLTs in mPCa. This expansion would unlock high commercial potential, given a therapy list price which ranges from approximately $95 thousand in the EU to over $200 thousand in the US when considering five doses per treatment episode.

Current and potential future positioning of RLTs in mPCa



The example of Pluvicto confirms the commercial attractiveness of the modality in mPCa. Launched in 2022 in the US, the product posted close to $1 billion in sales in 2023, despite facing shortage issues. Increasingly higher expectations for the product's peak sales highlight the optimism around the product and, indirectly, the modality. In early 2024, Novartis' guidance for Pluvicto peak sales was set at over $3 billion,[5] raised from over $2 billion[6] a year before, while some analysts forecast the product to potentially overcome the $4 billion peak sales mark.[7]

Pluvicto global sales, H2 '22-H1 '24, $m

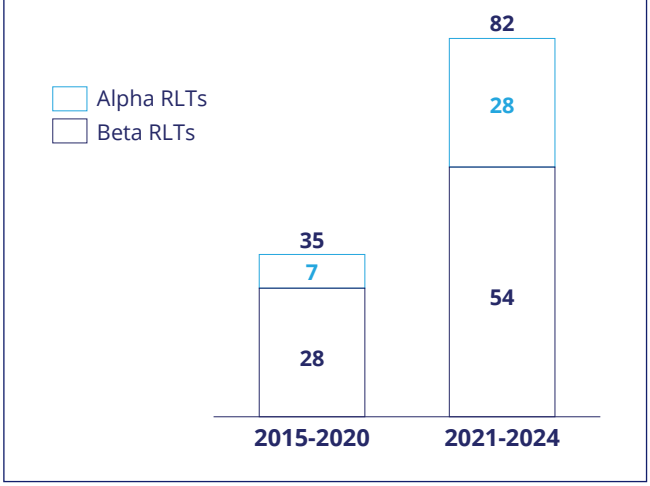


Note: [4]PSMAfore, SPLASH and ECLIPSE trials. [5]2024 J.P. Morgan Healthcare Conference Presentation; [6]2023 J.P. Morgan Healthcare Conference Presentation; [7]RBC February 2024 analyst report.

A Versatile Modality With Constant Innovation Bolstering Future Sustainability

While the most advanced RLTs in mPCa today are beta-emitting therapies (using ^{177}Lu), companies are now investigating the potential of RLTs that leverage an alpha emitter (mostly ^{225}Ac and ^{212}Pb). The underlying hypothesis is that alpha RLTs could display improved clinical performance versus beta RLTs, mainly because of the higher linear energy transfer to tumor cells. The result is a surge in alpha RLT candidates comprising the next generation of RLTs vs. the currently marketed (or close to market) beta RLTs from Novartis, Point Biopharma, and Curium. Combined with the intense research around ligand and chelator optimization, the RLT space is clearly experiencing unprecedented innovation.

Number of RLT clinical trials initiated in the US, Europe, Japan, Australia, and South Korea (2015-H1 2024): breakdown alpha vs. beta emitters



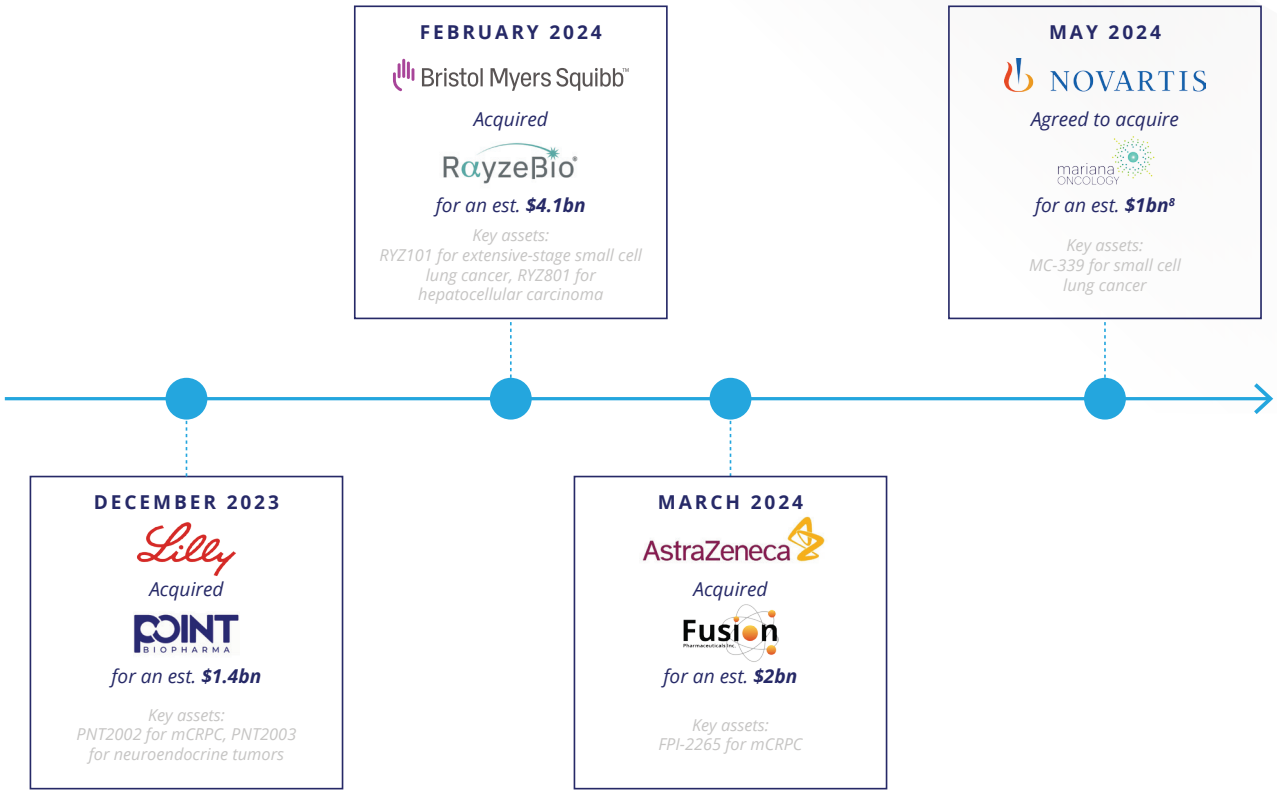
Snapshot on most advanced alpha RLTs in mPCa

Compound	Isotope	Company	Phase I	Phase II	Phase III
225Ac-PSMA-I&T/FPI-2265	^{225}Ac	Fusion Pharmaceuticals Inc.	Phase II/III		
CONV 01-alpha	^{225}Ac	Convergent Therapeutics	Phase I/II		
ADVC-001	^{212}Pb	AdvanCell	Phase I/II		
12 other products in Phase I			Phase I		

Recent deals confirm the soaring interest for the RLT modality, and in particular, for alpha-emitting candidates. AstraZeneca, Bristol Myers Squibb, and Eli Lilly all paid premium prices to acquire clinical stage RLT companies, with the most expensive acquisitions directed towards alpha RLT players (RayzeBio, Fusion Pharmaceuticals). The validation of the modality's proof of concept with Lutathera and Pluvicto and the expected superior clinical performance of alpha-emitting RLTs are likely driving modality-naïve big pharmas to seek a foothold in the space to drive their future growth in oncology. In addition, the RLT modality displays an attractive versatile

profile due to the ability to change the ligand so it can target other tumor-expressed proteins. Such platform potential represented by RLT players is probably another deciding factor behind the modality endorsement, as it potentially unlocks additional growth avenues.

Recent deals in the therapeutic radiopharmaceutical space



Conclusion

Today, mPCa is the most active space for the RLT modality. The metastatic setting encompasses numerous unmet needs in effective management. RLTs represent a viable treatment option, as demonstrated by their adoption in earlier lines of therapy and by the constant innovation on the most effective isotope and/or ligand to leverage. The recent mergers and acquisitions activity from modality-naïve giants is a testament to the high expectations for the technology, especially when leveraging alpha-emitters, as a meaningful growth contributor in oncology. However, a commercially successful RLT requires companies to account for numerous factors from an effective market access strategy, given high therapy prices, to efficient treatment logistics or isotope supply making every parameter of the specific and complex RLT value chain of utmost importance.

Note: [8]Upfront payment, not including potential milestone payments of up to $750 million.

About the Author

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Florent Chouvy has supported a wide portfolio of clients during his career, from early-stage biotech companies to mid-size and large pharmaceutical groups. His varied experience includes commercial due diligence, opportunity assessment, company and asset valuation, corporate and growth strategy, and health economics and outcomes research.

Florent's specialized areas of expertise encompass oncology, especially in nuclear medicine relative to both diagnostic and therapeutic applications and in immuno-oncology across main solid tumors, central nervous system, medical imaging, and sports medicine. Prior to joining Alira Health, he worked on mergers and acquisitions projects for Segula Technologies, an international engineering company, investigating French and cross-border deal opportunities. Florent graduated from Audencia Business School with a Master of Management in corporate finance.

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The development of radiopharmaceutical solutions, whether for diagnostics or therapeutics, is full of challenges. Companies must navigate diverse regulatory landscapes, a complex payer environment with high prices and cost pressures, and varying levels of nuclear medicine maturity across geographies.

Our team can accompany you on this complex development journey. We understand each step; from choosing the relevant regulatory pathway to delineating the reimbursement landscape and determining optimal clinical and competitive positioning of your product.

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- Unique service expertise that spans across the value chain, from CMC to market access, including regulatory services and strategy consulting
- An extensive track record of over 30 projects in nuclear medicine over the last 5 years, supporting from smaller research-driven players to industry-leading radiopharmaceutical companies