Research Strategy: Fredrik Y Frejd

How imaging created a path for breast cancer treatment

The emergence of radioligand therapies (RLTs) is changing the landscape of precision oncology. The approval of Lutathera in neuroendocrine cancer and Pluvicto in prostate cancer has demonstrated that radioactive drugs can selectively deliver radiation to tumours while limiting exposure to normal tissues, creating highly effective treatment options for diseases that have historically been difficult to manage.

Breast cancer is now attracting increasing attention from the radiopharmaceuticals field. HER2-directed antibodies and antibody-drug conjugates (ADCs) have transformed outcomes for many patients with HER2-positive disease, but resistance eventually develops and metastatic breast cancer remains incurable. While HER2 has long been recognised as an attractive target, no HER2-targeted radioligand therapy has yet reached the market.

Sweden-based Affibody AB recently reached an important milestone in the development of its HER2-targeted radioligand therapy, ABY-271, with the dosing of the first patient in Part B of its ongoing Phase I study in metastatic breast cancer. The advance builds on encouraging findings from the initial stage of the trial and represents the latest chapter in a scientific journey that began with a diagnostic imaging agent, ABY-025, now called tezatabep matraxetan.

The ABY-271 programme represents the culmination of more than two decades of work with Affibody molecules. However, the journey to ABY-271 did not begin with therapy but with an attempt to solve a different problem entirely: how to improve patient selection for HER2-targeted treatment.

When HER2-targeted therapies first entered clinical practice, receptor status was determined primarily through biopsy and immunohistochemistry. Although these approaches provide valuable information, they are limited by the fact that they sample only a single lesion. Increasing evidence suggested that metastatic tumours are often heterogeneous and that receptor expression can change as disease evolves.

The question was whether imaging could provide a more complete picture of HER2 expression throughout the body and thereby improve treatment decisions.

This led to Affibody's development of ABY-025, a small chemically synthesised HER2-targeting protein designed for PET imaging. Owing to its small size and high affinity, the tracer could produce images within hours after administration, overcoming one of the principal limitations associated with antibodies, which often require imaging several days after dosing.

Clinical studies subsequently showed that ABY-025 could quantify HER2 expression throughout the body and influence treatment decisions in a substantial proportion of patients. However, the programme also provided unexpected insights into the biology of metastatic disease. Investigations in HER2-low breast cancer revealed extensive heterogeneity both between patients and among individual lesions within the same patient. Some tumours classified as HER2-low exhibited considerable uptake, whereas others displayed very little target expression.

These observations highlighted an important limitation of current treatment paradigms. Patients with apparently similar pathology could differ markedly in their ability to benefit from HER2-directed therapies. At the same time, the emergence of ADCs such as Enhertu expanded treatment opportunities into HER2-low populations but also reinforced the importance of understanding which patients are most likely to benefit. Altogether, the imaging programme provided biological insights that pointed towards a new therapeutic opportunity.

Why radiotherapy?

The heterogeneity observed with ABY-025 raised questions about how best to treat tumours containing regions with varying levels of HER2 expression. Although ADCs have produced impressive results, their effects are largely restricted to the cells to which they bind and the immediate surroundings. Radioligand therapy offers a different mechanism. Radiation emitted from the radionuclide creates a so-called crossfire effect, whereby neighbouring tumour cells can also be destroyed even if they express lower levels of the target. This characteristic appeared particularly useful in heterogeneous tumours.

The imaging studies also suggested that patients classified within the HER2-low population are themselves highly heterogeneous. Some display target uptake approaching that seen in HER2-positive disease, whereas others have minimal uptake and may derive limited benefit from HER2-targeted therapies while still experiencing toxicity.

The concept of theranostics offered a way to address this challenge. A diagnostic agent could first identify patients with sufficient target expression, and a corresponding therapeutic version could then deliver high-energy radiation to those same lesions. In other words, if the target can be visualised, it can potentially be treated. These lessons provided the conceptual basis for developing ABY-271.

Transforming ABY-025 into a therapeutic candidate proved to be far more than a matter of attaching a therapeutic radionuclide. In many respects, diagnostic and therapeutic agents require opposite properties. For imaging applications, rapid tumour uptake and rapid clearance from the circulation are desirable. High contrast at a single time point is sufficient to generate useful images and any remaining diagnostic radioactivity usually disappears quickly without causing harm.

Therapeutic applications are fundamentally different. Here, the important parameter is cumulative exposure over time. To achieve a therapeutic effect, radiation delivered to the tumour must exceed that delivered to normal tissues.

Moreover, therapeutic radionuclides such as lutetium-177 possess half-lives measured in days rather than hours. Consequently, the targeting molecule must remain associated with tumours long enough to exploit the radioactive payload while minimising toxicity elsewhere. The challenge, then,

became one of molecular engineering.

Affibody molecules occupy a position between antibodies and peptides. Derived from a robust three-helical protein scaffold comprising only 58 amino acids, they combine high affinity and selectivity with the favourable tissue penetration characteristics associated with smaller proteins. The original ABY-025 molecule was optimised for rapid imaging. To create a therapeutic agent, its kinetic profile had to be altered. The solution was to exploit albumin, the most abundant protein in blood plasma. Albumin circulates widely throughout the body and distributes into tissues more readily than antibodies. By introducing albumin association, it became possible to improve the tissue distribution of the molecule, to increase tumour exposure and reduce rapid renal elimination.

This strategy, pioneered by Affibody nearly two decades ago, has since attracted broader interest across the field. Importantly, the approach has been clinically validated through other Affibody programmes. Experience with the Phase 3 anti-IL-17 candidate izokibep, which has been studied in more than a thousand patients, has provided extensive information regarding safety, tolerability and the behaviour of albumin-associated constructs. This clinical experience substantially reduced the risks associated with applying the same principles to radioligand therapy.

The resulting molecule, ABY-271, combines HER2 targeting with albumin binding and a therapeutic radionuclide payload.

Before entering the clinic, the programme underwent extensive preclinical evaluation. Studies demonstrated preferential tumour accumulation together with favourable distribution in normal tissues. Dosimetry modelling and translational calculations were performed to estimate radiation exposure in humans and suggested that clinically meaningful doses could be achieved. Encouragingly, emerging human data appear to support these predictions.

Initial assessments performed in the first patients dosed showed effective tumour targeting and confirmed the favourable biodistribution profile anticipated from the preclinical work. Particularly noteworthy was the low uptake observed in kidneys. While kidney accumulation had been prominent with the imaging agent, engineering the therapeutic molecule changed its distribution profile in a manner consistent with the original design objectives. These findings provide confidence to proceed to formal dose escalation.

Unlike conventional drugs, radioligand therapies involve several variables that require optimisation. In addition to the amount of radioactivity administered, investigators must consider the amount of carrier molecule and ultimately the dosing schedule. The ongoing study therefore incorporates an integrated escalation strategy designed to evaluate both protein dose and radioactivity simultaneously. This approach reflects long-standing expertise in radiopharmaceutical development and aims to establish a robust foundation for later-stage studies.

Future development will focus on defining the optimal therapeutic window and subsequently refining dosing regimens in accordance with evolving regulatory expectations.

The transition from ABY-025 to ABY-271 reflects more than the evolution of a single molecule. It illustrates how insights gained from molecular imaging can inform the design of entirely new therapies.

Clinical experience with ABY-025 revealed the extent of heterogeneity within HER2-expressing tumours and highlighted the limitations of relying solely on biopsy-based assessment. These observations, together with the emergence of HER2-low disease as a clinically relevant entity, pointed towards the potential advantages of a theranostic approach in which diagnostic imaging and therapy are intrinsically linked.

The development of ABY-271 required a different set of molecular properties from those needed for imaging. Through engineering of albumin association and extensive translational modelling, Affibody has sought to create a radioligand capable of delivering prolonged tumour exposure while maintaining a favourable distribution profile.

Early clinical findings from the first-in-human study have supported these design principles, demonstrating tumour targeting and low uptake in kidneys and other critical organs. In May 2026, the programme reached another important milestone with dosing of the first patient in Part B of the Phase I study. This stage of development will evaluate higher levels of radioactivity together with additional protein mass doses in patients with more advanced HER2-positive metastatic breast cancer. The results are expected to further define the therapeutic window and guide subsequent clinical development.

Part B will enrol 15 patients with progressive disease following at least three prior lines of systemic therapy. By integrating escalation of both radioactivity and protein dose, the study is designed to provide a detailed understanding of the relationship between these variables, an approach intended to optimise the therapeutic profile from the outset.

More broadly, the programme demonstrates how nearly two decades of work on albumin-binding technology, together with the biological insights generated by ABY-025, have converged in a new generation of radioligand therapies.

New generation of radioligand therapies

As radiopharmaceuticals continue to expand beyond prostate and neuroendocrine cancers, HER2-expressing tumours may represent one of the next major opportunities. The progression from ABY-025 to ABY-271 suggests that small, engineered scaffold proteins could provide an important bridge between diagnosis and therapy, bringing the promise of precision medicine closer to routine clinical practice.

The development of ABY-271 illustrates how diagnostic imaging and therapy can reinforce one another. Insights gained from ABY-025 not only improved understanding of tumour heterogeneity but also highlighted the potential advantages of radiotherapy in HER2-expressing cancers.

More broadly, the programme demonstrates the versatility of the Affibody scaffold itself. Originally described in 1997, the technology has evolved into a platform capable of supporting applications ranging from molecular imaging to cytokine blockade and radiopharmaceutical development.

The current clinical results with ABY-271 represent the latest stage in that evolution. What began as an effort to improve treatment selection has become an opportunity to deliver treatment itself.

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