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PRODUCT DEVELOPMENT

Radiotherapy blasts forward

BY KAREN TKACH TUZMAN, ASSOCIATE EDITOR

High-wattage takeouts and commercial launches have revived interest in radiopharmaceuticals for cancer. The challenge for the new wave of candidates is to achieve enough differentiation to justify the logistical hurdles of manufacturing and delivering products that rapidly decay.

The excess nuclear energy released by radioisotopes as they decay to a more stable state can be harnessed to detect *in vivo* signals, or to kill pathogenic cells by inducing DNA damage.

While radiotracers are ubiquitous as diagnostic tools and external radiation therapy is a routine part of cancer treatment, systemic radiotherapies have lagged because they are more challenging to produce and deliver, and the first approved products lost out to more convenient alternatives.

The field quietly picked up steam, however, via improvements in supply chain infrastructure and tumor-targeting technologies, along with promising proof-of-concept signals from small compassionate use trials.

That progress paid off when Bayer AG (Xetra:BAYN) and Novartis AG (NYSE:NVS; SIX:NOVN) each spent billions of dollars to acquire radiotherapies developed by small European biotechs.

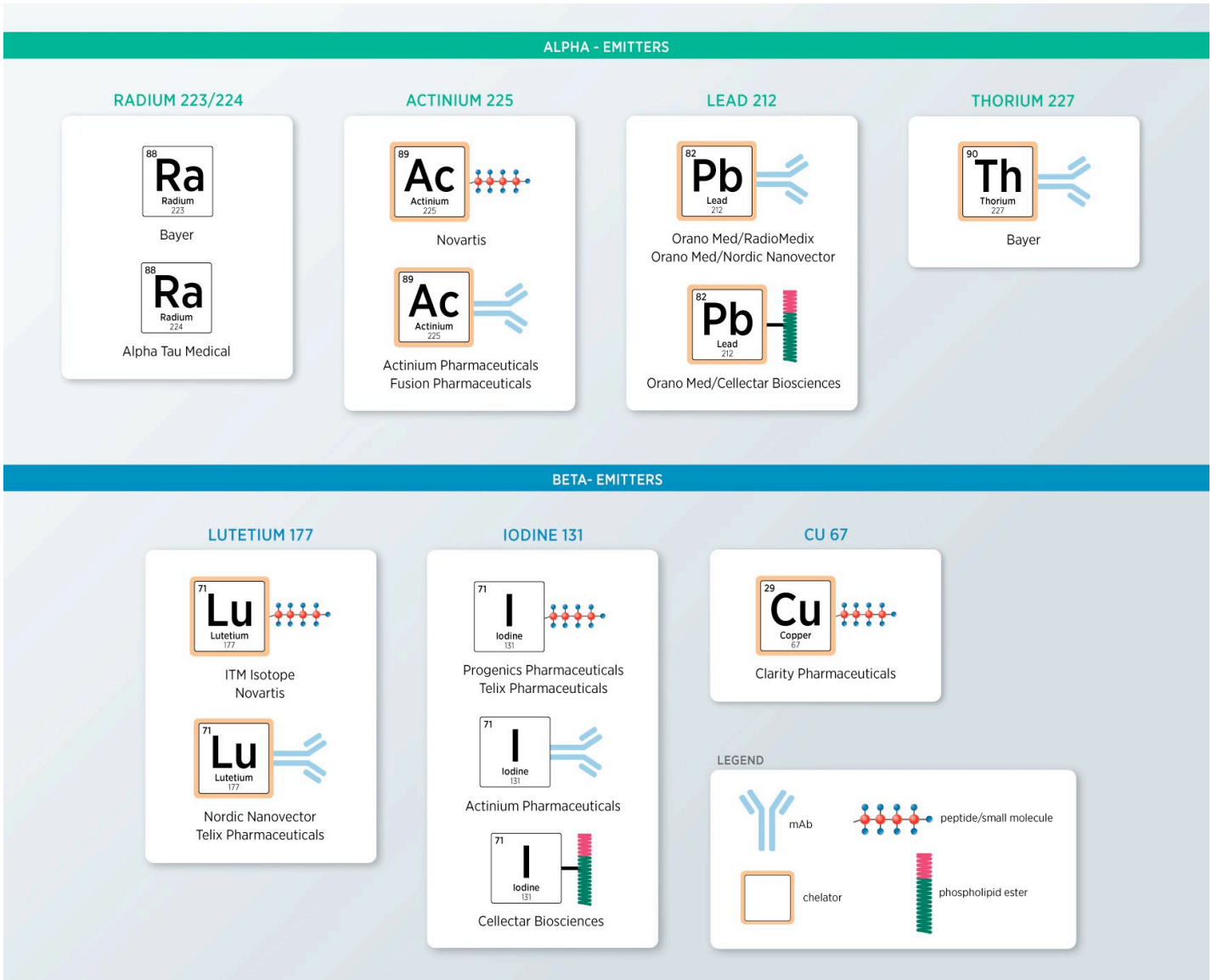
Bayer bought Norwegian biotech Algeta ASA for $2.9 billion in 2013, gaining the radium 223-based Xofigo. The drug is approved to treat castration-resistant prostate cancer (CRPC) patients with symptomatic bone metastases and no known visceral metastatic disease.

Novartis acquired French company Advanced Accelerator Applications S.A. (AAA) for $3.9 billion in 2017, gaining the lutetium 177-based neuroendocrine tumor drug Lutathera.

A year later, Novartis acquired Endocyte Inc. for $2.1 billion, obtaining 177Lu-PSMA-617, a radiotherapy in Phase III testing for PSMA-positive metastatic CRPC due to read out in 2020. Endocyte had bought 177Lu-PSMA-617 from German biotech ABX GmbH in 2017 for $177.6 million in total deal value.

Radiotherapy War Chest

The latest generation of radiopharmaceuticals in company pipelines is broadly divided according to whether the compounds incorporate radioisotopes that emit alpha particles versus those that emit beta particles. Companies are also adopting different targeting strategies to direct radioisotopes to tumor sites, which includes attaching them to peptide or small molecule ligands, mAbs or phospholipids that interact with targets on tumor cell surfaces. In order to link targeting ligands to actinium 225, lead 212, thorium 227, lutetium 177 or copper 67, companies must first cage the radioisotopes using molecular structures known as chelators. Iodine 131-based therapies do not require chelators to be linked to targeting ligands. Because radium cannot be directly linked to targeting ligands, and no chelators exist for the element, radium-based therapies either rely on the element's natural bone-homing properties or require intratumoral delivery.



Novartis highlighted Lutathera as a bright spot in its 3Q19 earnings, reporting that it brought in $119 million in revenue, a 116% growth over 3Q18.

"People are looking at Lutathera and saying, 'wow, we need to take this seriously again,'" Sandesh Seth, CEO of radiotherapy play Actinium Pharmaceuticals Inc. (NYSE-A:ATNM), told BioCentury.

Bayer and Novartis are now building early-stage pipelines that expand into other targets and radioisotopes. In parallel, at least nine biotechs are growing the radiotherapy armamentarium using a range of radioisotopes, targeting ligands, linkers and chelators -- chemical groups used to "cage" certain radioisotopes and prevent them from breaking off in circulation (see Figure: "Radiotherapy War Chest").

Companies are also exploring combinations with DNA damage response inhibitors that weaken cancer's ability to withstand radiotherapies, and immuno-oncology agents that capitalize on radiotherapy-induced immunogenic cell death.

"You have to pick your indications carefully, because there is that little extra inconvenience that can become a huge barrier if there's no differentiation," said Seth.

While personalized manufacturing was a major headwind for the first systemic radiotherapies approved in the early 2000s, the rise of autologous cell therapies has made the paradigm more widely accepted, he said.

"Radiotherapy 1.0 were good drugs, but commercially they were a problem," Seth said. "There was a big disenchantment with radiotherapy because it's just-in-time, personalized medicine. Now, we're in a different age."

These early therapies include the yttrium 90-labeled anti-CD20 mAb Zevalin ibritumomab, which Aurobindo Pharma Ltd. (NSE:AUROPHARMA; BSE:524804) markets to treat non-Hodgkin's lymphoma (NHL), and the iodine 131-labeled anti-CD20 mAb Bexxar tositumomab from GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), which was approved to treat NHL in 2003 but discontinued in 2014 due to limited use.

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While clinical experience suggests systemic radiotherapies can be safe, the safety profiles of specific radioisotopes and compounds are still being worked out.

In 2017, Bayer stopped a Phase III trial of Xofigo in metastatic CRPC patients after reporting more fractures and deaths vs. placebo. The trial was testing Xofigo in combination with the CYP17 inhibitor Zytiga abiraterone acetate abiraterone and prednisone/prednisolone.

As the players choose their strategies, they are weighing both logistical issues such as supply chain accessibility, and technical considerations such as matching radiation path length to tumor type, and aligning radioisotope half-lives to compounds' overall PK.

Nuclear facility

Because radiotherapies decay with half-lives of days, manufacturing and distribution must be done on demand for individual patients. That sets a high bar in terms of the resources required to get products to patients, and the need to demonstrate value relative to available off-the-shelf therapies.

The manufacturing hurdles for systemic radiotherapies have been steeper than for diagnostic radiotracers, Germo Gericke, head of R&D for Novartis' AAA unit, told BioCentury.

That's because the radioisotopes used in diagnostics can be made in generators or cyclotrons, which are about the size of an espresso machine and a microbrewery, respectively. In contrast, the radioisotopes used in radiotherapies require more energy to activate and are typically made in nuclear reactors, which are fewer and farther between, meaning the material must be shipped over longer distances.

In the case of Lutathera, which has a half-life of 6.7 days, once the radioisotope is produced in a nuclear reactor, it must be linked to its targeting ligand under sterile conditions, undergo QA and be shipped to the patient within two to three days.

AAA chairperson and president Sidonie Golombowski-Daffner told BioCentury that improvements in manufacturing efficiency and proliferation of radiotherapy manufacturing companies are helping the space take off. She thinks the combination of AAA's radiotherapy manufacturing expertise and supply chain with Novartis' drug

development infrastructure gives the company an advantage as it expands its global footprint.

Smaller companies like Israel's Alpha Tau Medical Ltd., whose radium 224-based therapy has a 3.6 day half-life, may have to opt for a more localized strategy. Company spokesperson Sara Jaehnert said the company plans to build manufacturing plants in proximity to major target markets. Alpha Tau has an active manufacturing site in Israel and is finalizing construction of a plant in the Boston area. It also plans to manufacture in Japan and Europe.

Choose your weapon

The first choice companies have to make is whether to develop compounds that emit alpha particles, which release more energy over shorter distances, or those that emit less powerful beta particles over longer ranges. While some companies have planted a flag on one side of the divide, at least two are developing both (see Table: "Alpha and Beta Emitter Pipelines").

Bayer's radium 223-based Xofigo was the first alpha-emitter on the market. Other alpha-emitting radiotherapies in development incorporate actinium 225, lead 212 or thorium 227.

Radiotherapies incorporating beta-emitting isotopes -- which include lutetium 177, iodine 131, copper 67 and yttrium 90 -- have a longer clinical history going back to the Zevalin and Bexxar approvals.

The advantage of alpha-emitters is that they produce double-stranded breaks in DNA, which are harder for a cell to survive than the single-stranded breaks induced by beta-emitters, said Dominik Mumberg, VP of therapeutic area oncology and targeted alpha therapies in Bayer's research organization.

Alpha- and beta-emitter pipelines

At least 12 companies have disclosed they are developing radiotherapies that are delivered systemically or intratumorally. The tables show lead and pivotal-stage alpha-emitting and beta-emitting radiotherapies. *Source: Company websites*

Alpha emitters

Radioisotope	Company	Product	Status	Target	Indication
Radium 223	**Bayer**	Xofigo radium Ra 223 dichloride	Mkt	NA	Castration-resistant prostate cancer (CRPC) with sympotomatic bone metastases
Actinium 225	**Actinium**	Actimab-A (actinium Ac 225 lintuzumab)	Ph II	CD33 (SIGLEC3)	Acute myelogenous leukemia (AML)
	Fusion	FPI-1434	Ph I	Insulin-like growth factor-1 receptor (IGF1R; CD221)	Solid tumors
	Novartis	225 Ac-PSMA-617	Preclin	Prostate-specific membrane antigen (PSMA; FOLH1; GCPII)	Prostate cancer
Radium 224	**Alpha Tau Medical**	Alpha DaRT	Pilot	NA	Solid tumors
Lead 212	**Orano Med /RadioMedix**	Alphamedix (ORM2110)	Ph I	Somatostatin receptors	Neuroendocrine tumors
Thorium 227	**Bayer**	CD22-TTC (BAY 1862864)	Ph I	CD22	CD22-positive non-Hodgkin's lymphoma (NHL)
	Bayer	MSLN-TTC (BAY 2287411)	Ph I	Mesothelin	Mesothelin-expressing solid tumors
	Bayer	PSMA-TTC (BAY 2315497)	Ph I	PSMA	Metastatic CRPC

Beta emitters

Radioisotope	Company	Product	Status	Target	Indication
Lutetium 177	**Novartis**	Lutathera lutetium Lu 177 dotatate	Mkt	Somatostatin receptors	Neuroendocrine tumors
	ITM Isotope	Solucin 177Lu-edotreotide	Ph III	Somatostatin receptors	Neuroendocrine tumors
	Novartis	177Lu-PSMA-617	Ph III	Prostate-specific membrane antigen (PSMA; FOLH1; GCPII)	Castration-resistant prostate cancer (CRPC)
	Nordic Nanovector	Betalutin 177Lu-satetraxetan-lilotomab (Betalutin)	Ph I/II	CD37	Non-Hodgkin's lymphoma (NHL)
	Telix	TLX591 (177Lu-DOTA-rosopatamab)	Ph II	PSMA	CRPC
Iodine 131	**Progenics**	Azedra iobenguane I 131	Mkt	Norepinephrine transporter	Neuroendocrine tumors
	Actinium	Iomab-B (apamistamab-I-131)	Ph III	CD45	Bone marrow transplant conditioning
	Cellectar	CLR 131	Ph II	Lipid rafts on tumor cell surfaces	B cell lymphoma; multiple myeloma (MM)
	Telix	TLX101 (4-iodo-[131I]-phenylalanine)	Ph I	Solute carrier family 7 member 5 (SLC7A5; LAT1)	Glioblastoma
Copper 67	**Clarity**	Sartate	Ph I/II	Somatostatin receptor 2 (SSTR2)	Meningioma

A 2016 clinical study in *Journal of Nuclear Medicine* suggests targeted alpha-emitters can overcome resistance to beta-emitters linked to the same targeting ligand.

However, the fact that the radius of beta particles is on the scale of millimeters, versus the microns traveled by alpha particles, can be a benefit for some applications. For example, in more heterogeneous tumors, beta particles could travel far enough to kill surrounding tumor cells that don't express the target ligand, boosting efficacy, said Golombowski-Daffner.

Different beta-emitters can also be differentiated by their path lengths. For example, clinical experience suggests yttrium 90 has more toxicity that lutetium 177, likely due to its longer path length, but that same property might make it better suited to tumor types that require deeper penetration, said AAA's Gericke.

Actinium's Seth said the greater damage caused by alpha-emitters raises the bar on targeting specificity.

According to Gericke, the observed "recoil" from releasing alpha particles can cause the radioisotope to fall out of its chelator cage, creating the potential for systemic exposure.

But not every radiotherapy incorporates a chelator.

Researchers have been unable to develop a chelator capable of containing radium, meaning the radioisotope cannot be linked to a targeting ligand. As a result, its clinical applications have been limited to those that align with the element's natural tropism for bone, as is the case for Bayer's Xofigo, or systems such as Alpha Tau's that directly deliver the radioisotope to tumor tissues.

Alpha Tau's Alpha DaRT therapy consists of an intratumorally implanted scaffold with radium 224 atoms fixed to its surface. The energy released when the radium 224 decays to radon 220 releases the radioisotopes into tumor tissue. They then disperse via diffusion and convection.

By contrast, the inability to chelate radium led Bayer to focus on thorium 227 for its next generation of compounds, said Mumberg. "We can now

use thorium as a radioactive payload and add that to a targeting moiety, allowing us to address many different tumor types."

The company's pipeline of Targeted Thorium Conjugates (TTC) includes three Phase I agents targeting PSMA, mesothelin and CD22, respectively, along with a preclinical compound against HER2. Mumberg said Bayer opted for thorium 227 over other alpha-emitters because its half-life matches that of the company's antibodies, and it is derived from the same radioisotope as radium 223. That means thorium's downstream radioactive "decay chain" would be the same as Xofigo's, and Bayer could use the same supply chain.

Novartis and Actinium Pharmaceuticals both have actinium 225 programs in development. Orano Med LLC is focusing on lead 212-based therapies, including a Phase I program partnered with RadioMedix Inc.

Among the beta-emitters, lutetium 177 and iodine 131 are the dominant radioisotopes in company pipelines.

Lutetium 177 requires a chelator to be linked to targeting ligands, while iodine 131 can be directly linked to peptides, small molecules, antibodies or other targeting domains, such as the phospholipid ether (PLE) vector developed by Cellectar Biosciences Inc. (NASDAQ:CLRB), which targets lipid rafts on cancer cell membranes.

Ligand factors

Another variable is the choice of targeting ligand, where the primary split is between mAbs and peptides or small molecules that mimic peptides.

mAbs have longer half-lives, which, depending on the application, can be an advantage or a safety liability.

Gericke said the choice of radioisotope and targeting ligand comes down to a "triangle of three variables": the radiosotope's half-life, the compound's residence time in the tumor, and its persistence in circulation.

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"You want a big area under the curve of radiation at the tumor site, and a very small area under the curve for organs that are radiosensitive, such as the bone marrow, kidney and gut," he said.

Actinium is going the mAb route. The company's Actimab links an anti-CD33 mAb to actinium 225. According to Seth, the radioactive warhead decreases the half-life of the mAb from about three weeks to three days, which cuts down the risk of toxicity due to long-term exposure.

The compound is in Phase II testing for AML and Phase I testing for other hematological cancers; Actinium also has Iomab, an anti-CD45 mAb linked to iodine 131, in Phase III testing for pre-transplant conditioning and Phase I testing for conditioning before delivery of cell and gene therapies.

Novartis has so far focused on small molecule targeting ligands because the pharmacokinetics align with the company's primary radioisotope. "Small molecules have a shorter half-life, and are usually excreted through the kidney. That matches up better with the half-life of our current therapeutic workhorses like lutetium, but we are open to other ligand structures," said Gericke. bc

TARGETS

HER2 (EGFR2; ErbB2; neu) - Epidermal growth factor receptor 2

PSMA (FOLH1; GCPII) - Prostate-specific membrane antigen

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