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Inside Bayer Oncology: An Interview With Robert LaCaze

by Chris Morrison

Bayer AG may more often make headlines for its deal-making in consumer health and agriculture, but the massive German conglomerate sees oncology drugs as a key engine of future success within its high-growth pharmaceuticals business. A Q&A with Robert LaCaze, EVP of Bayer's new Oncology Strategic Business Unit.

Robert LaCaze joined *Bayer AG* in October 2015 from *Bristol-Myers Squibb Co.*, where he was head of product and portfolio strategy, to help lay the foundation of Bayer's oncology strategic business unit that went into effect in February 2017. LaCaze was tapped as the unit's first leader, combining Bayer's strategic oncology operations, regulatory affairs, clinical development, marketing, medical affairs, pricing and access functions in a single organization to accelerate development and commercialization of new cancer therapies.

Bayer is not a top-10 oncology company, and LaCaze avoids too specifically pinning down the firm's aspirations in biopharma's biggest market. Instead, he points to the vastness and the heterogeneity of opportunities within the oncology space, suggesting that even a second-tier cancer company can achieve significant growth if it plays to its own strengths and knows how to stay focused.

Over the past several years, Bayer has indeed pulled together a small handful of platforms for future growth in the oncology area, building up its antibody-drug-conjugate technology and acquiring the radiopharmaceuticals specialist *Algeta ASA* for $2.6 billion in December 2013. *[See Deal]*These assets complement Bayer's strength in small-molecule targeted cancer therapies, such as its marketed multikinase inhibitor *Stivarga* (regorafenib) or the promising PI3k inhibitor copanlisib, which is under priority review at FDA to treat certain lymphomas. The company has yet to make a big splash in the increasingly important immuno-oncology space, but LaCaze is confident that by eschewing first-generation immuno-oncology assets such as anti-PD-1 therapies, Bayer can position itself for the next wave of IO growth. To that end the company has

allied with the Israeli biotech *Compugen Ltd.[See Deal]* for that business' next-generation checkpoint inhibitors.

The moves Bayer has made outside oncology – outside its pharmaceutical business entirely – dwarf deals like the Algeta acquisition and greatly diminish the potential for any expensive moves in the oncology area. In October 2014, Bayer paid *Merck & Co. Inc.* $14.2 billion to acquire a portfolio of consumer health assets. And the company is currently in the midst of a $66 billion acquisition of agriculture giant *Monsanto Co.*, as well as reducing its stake in the materials science company Covestro AG, which spun out of Bayer in 2015. But regardless of the massive deal-making elsewhere in the conglomerate, LaCaze notes the ongoing success of Bayer's pharmaceuticals business and the central role oncology plays within that group.

In Vivo interviewed LaCaze at the *BIO International Convention* in San Diego in late June. In a wide-ranging discussion, LaCaze talked about the importance of being focused within oncology, Bayer's oncology platforms, and why oncology is increasingly a key priority at the massive conglomerate.

In Vivo: Why is the strategic business unit the right structure for oncology within Bayer's pharmaceuticals group? How does the SBU operate?

A Robert LaCaze: The business unit itself is in place to make rapid decisions and also be able to get medicines to patients as quickly and prudently as possible. Rapid decisions still need the right rigor – we want to make sure as we move forward that we understand the science and our customer base and bring important medicines that are highly differentiated to the marketplace.
And this isn't an approach that would necessarily work in other areas of our pharmaceutical business. In oncology there's an established regulatory approval process where you can move from Phase II into regulatory approval, or Phase I directly into Phase III. You can't typically do that in cardiovascular disease. If you look at cardiovascular disease trials, there can be ten to twenty thousand patients, so it's very different. In oncology there's this massive amount of innovation, and so much competition, to compete you need to move quickly and decisively.

Once we agreed to the strategic approaches we wanted to take, then the question became how do we best implement those strategies we've agreed to as a company, the approaches we want to take, and where we want to be. It quickly became obvious that a very focused organization in oncology was going to be a good approach,

especially as you think about who we're competing against.

We're in the oncology market with several large pharma companies, but we're also competing with smaller oncology-focused biotechs with different structures. We kind of have a hybrid between those two different types of approaches, one that fits the needs that we have. Importantly, we wanted to make sure we were appropriately focused. When you look at the therapeutic area, it's the largest growth therapeutic area, it's the fastest growing area, but it's very segmented. Nobody really owns a big piece of all the different platforms and technologies. And it's an area that's rapidly changing. We know that half of the breakthrough designations from the Food and Drug Administration are given in oncology. And that 35% to 40% of all the Phase Is in development across industry are in oncology. So you really need to focus in the areas where you choose to compete if you want to be successful in this space.

Q **What are the areas in oncology where Bayer is choosing to focus? How do you make those decisions, based on your current portfolio and the lure of exciting areas like immuno-oncology?**

A We think about it in terms of where we want to play to win, in terms of our resources and investments. Which platforms do we want to focus on, and which tumor types do we want to focus on. As we think about the platforms for example, strategically as a company we have a good pipeline. It's one of the things that attracted me to Bayer in the first place. But in terms of the focus, as opposed to being too diluted across too many different platforms, we decided to focus on four different key areas.
The first oncology area where we're really good as a company is our targeted small-molecule approach. Cell cycling, cell signaling and tying in the pharmaco-diagnostics early on, a priori, before we move to first-in-humans. We're trying to figure out the biomarker approach with these small molecules as we move forward, and focus on developing first-in-class treatments.

Our second area of focus is our antibody-drug-conjugate platform and our ADC technology. We have a compound in clinical development and many preclinical-stage compounds in the ADC space. (Also see "*Cancer's Next-Gen Smart Bomb: Who Will Be*

First To Weaponize?" - In Vivo, 22 May, 2017.)

The third area is around our targeted alpha therapies. And obviously we have *Xofigo* [radium-223 dichloride, approved for treating patients with castration-resistant prostate cancer who have bone metastases] in the market currently but we have a whole platform with our acquisition of Algeta, our thorium platform (thorium degrades into radium, which is what our Xofigo is). But you can also actually take thorium and conjugate it with a linker, and target it like an ADC. That platform is highly differentiated for us as a company. If the platform continues to prove successful – the science is still early, we're in Phase I with one of our compounds and have several more moving into Phase I over the next few quarters – but if successful, it offers many opportunities.

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A As a company we want to be focused on the second-generation, second wave of immuno-oncology. That first wave of checkpoint inhibitors, specifically antibodies against PD-1 and CTLA4, are very important compounds. But we don't want to be the seventh or eighth company out with a PD-1 inhibitor. And also when we look at the science, we know that about seven out of 10 patients won't respond to a PD-1 inhibitor, with the possible exception of melanoma patients. But even within 12 months, unfortunately about 80% to 90% of those patients will need additional treatment options due to progression. The first-wave immuno-oncology drugs do benefit patients and there's a subset of patients who will receive a long-term benefit. But it's still a huge unmet medical need and we need a second-generation approach

> to immuno-oncology. The question we're asking is how do you turn what we call a "cold" tumor into a "hot" tumor, susceptible to an attack from the immune system. There are several ways to do that. It could be an immuno-oncology approach, it might be a targeted therapy approach, it might be a radiopharmaceutical approach. The tumor is "cold" because T cells aren't infiltrating the tumor; and using something to damage the tumor, an "IO-IO" approach or otherwise, is necessary. We're not disclosing the targets we're going after just yet, but we have some unique approaches and we're looking at both biologics and small-molecule strategies. It's still early.
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> When you look at our pipeline, we have gone from a one-drug company 10 years ago, *Nexavar*, with two indications, to today, three drugs on the market with seven indications. And hopefully by 2019 or 2020 we'll have additional drugs on the market, in additional indications. So we really are growing as an oncology company. (*See Exhibit 1.*)

Exhibit 1

Drug Name	Disease	Status
entinostat	Cancer, breast	Phase III
Darolutamide (licensed from Orion)	Cancer, prostate	Phase III
roniciclib	Cancer, lung, small cell	Phase II
Refametinib (licensed from AstraZeneca)	Cancer, colorectal	Phase II
anetumab ravtansine	Cancer, solid, unspecified	Phase II
rogaratinib	Cancer, bladder	Phase I
Pasotuxizumab (licensed from Amgen)	Cancer, prostate	Phase I
lupartumab amadotin	Cancer, squamous cell	Phase I
epratuzumab-thorium-227	Cancer, lymphoma, non-Hodgkin's	Phase I
BAY-1895344	Cancer, solid, unspecified	Phase I
BAY-1436032	Cancer, solid, unspecified	Phase I
BAY-1251152	Cancer, solid, unspecified	Phase I
BAY-1217389	Cancer, solid, unspecified	Phase I
BAY-1179470	Cancer, solid, unspecified	Phase I
BAY-1161909	Cancer, breast	Phase I
BAY-1143572	Cancer, unspecified	Phase I

BAY-1125976	Cancer, breast	Phase I
BAY-1082439	Cancer, solid, unspecified	Phase I

Source: Pharmaprojects | Pharma Intelligence, 2017

Q **Bayer has highlighted Xofigo as an example of the kind of innovation the company will pursue in oncology, and it's a cornerstone of one of the four platforms you just highlighted. It's not an ordinary drug, so how's it performing?**

A Obviously, as you come into the market with a drug like Xofigo, there's a lot to learn. You have to establish the distribution and the connectivity between the oncologists and the urologists and the radiation oncologists, and so it takes a bit longer to get it going. Country by country these distribution systems and relationships vary greatly. It's complex and that's why every account is different. And that's part of the pleasure of working in that area but also part of the challenge.

But Xofigo is doing very well in the marketplace. [In the second quarter of this year total revenue for the drug reached $105 million, a 30% increase over the prior year.] We are well ahead of where we thought we'd be in Japan, where the drug was only launched in May 2016. We're having tremendous growth in the US, in parts of Europe, and it's one of those things that when people understand it, where and how to utilize it with patients, it's going to grow. The drug is given over six cycles, and you want patients to get as close to those six cycles as possible. If they use the drug too late, patients may not receive enough of the drug to have the overall survival benefit. You want to use it earlier in the lines of therapy, and then patients can receive the five or six cycles. And patients do a lot better when they get more of the drug, partially because of the drug, partially because they're earlier in the cycle of the disease, so you can have that positive impact for the patient.

We actually have completed a trial with Xofigo with abiraterone [*Johnson & Johnson*'s *Zytiga*] in earlier stages of prostate cancer with bone metastases. We're waiting for the results, it's a results-driven trial. The enrollment has completed and we have announced that we should have the data sometime next year.

Q **Bayer is a diversified company, and other parts of the business must consume a lot of resources and attention – particularly as the company is working to close the $66 billion Monsanto acquisition. How does oncology, which is relatively small, maintain an adequate share of voice?**

A Those other businesses are important, but they're individual business units. The new Bayer, the way we're set up, our head of crop sciences, head of consumer, head of pharma are all part of the board of management. Within the pharmaceuticals business, our key growth is coming from cardiovascular therapies and from oncology, and there continues to be tremendous opportunity in oncology. Remember, that the oncology market itself is the fastest growing market, and it's also the largest market. Oncology is also a very diverse market, so we can focus on those areas where we are strong as a company. Again, immuno-oncology is an important area, but there remains a huge unmet medical need. And we feel that we have a differentiated approach with our ADC, alpha-therapy, and small-molecule platforms, in addition to what we are developing in immuno-oncology.

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Our funding hasn't gone down in oncology. It continues to be increased. And R&D for pharma is a major growth driver for us as a company, probably the largest part of our overall growth. And so it's not hard to deduce that if you want to be in pharma, it is important to leverage your oncology expertise. And to do that, we need to be focused on our areas of differentiation. We created the oncology strategic business unit to drive this process.

Q **How are you equipping the oncology strategic business unit to compete in the emerging value-based care paradigm?**

A Part of the reason for establishing the oncology strategic business unit is that we wanted to make sure we could move fast but with rigor. We have a head of oncology development that has both late-stage and early-stage clinical operations and regulatory affairs reporting in to that person. But it was important not to just have the clinical component of it, we needed to emphasize market access. The head of market access and pricing for oncology sits in the business unit as well, reporting directly to the head of the business unit. The head of medical affairs for oncology is in the business unit and a lot of the real-world evidence medicine is done through our medical affairs organization. Now you have both market access and medical affairs as the main drivers of establishing our therapies' value, setting the endpoints for, and shaping, the trials we need to conduct to demonstrate value.

Everything we're doing right now, even early on, we're incorporating the real-world evidence approaches. We want to make sure we're collecting the right data in our clinical trials so we know how these drugs are utilized in real life. That's an imperfect science, and it's difficult. But you have to implement it. We're spending quite a bit of investment on collecting that type of data across our major brands and our new brands that are coming.

Q **How does the oncology unit fit alongside some of the priority business functions you'll need to grow the portfolio, for example business development?**

A Business development is outside the oncology business unit, but we have people in BD dedicated to oncology. We have early- and late-stage oncology business development, and somebody within the business unit at the senior leadership team that works with early- and late-stage BD to make sure the strategies are tight and the partnerships we're evaluating stay aligned with our core oncology strategies. Because we have many good drug candidates in our pipeline the opportunities have to add value. But we do partner a lot, as no one company has all the answers.

Take our deal with *Orion Corp.* for example, around the androgen receptor inhibitor

darolutamide. [Bayer paid €50 million up front to license worldwide rights to the then-Phase II compound in 2014*[See Deal]*.] That compound is in Phase III development and one of the important differentiators is that it doesn't cross the blood-brain barrier and so may have a more competitive adverse event profile. The Algeta acquisition also brought us a differentiated strategic platform. And we also have an immuno-oncology partnership with Compugen and partnerships with the Broad Institute and the German Cancer Research Center where we're looking at early preclinical assets that may be future candidates for clinical development.

I'm also in constant contact with the Bayer LifeScience Center, our innovation unit that has made key investments in our CRISPR joint venture *Casebia Therapeutics* and our stem cells joint venture *BlueRock Therapeutics*. *[See Deal][See Deal]*Oncology isn't part of those deals as of right now – they're focused on cardiology and hematology, as well as ophthalmology. But we're looking for oncology opportunities as well. The idea behind the Bayer LifeScience Center and those ventures is to be able to run with innovation as quickly as possible.

Q **And what about the broader commercial organization – how can the oncology strategic business unit better leverage Bayer's global footprint in places like Asia?**

A We have a broad global footprint now as a company. In addition to the US and Europe, we consider markets like China and Japan to be focused markets for us as a company. And they're very important markets for us in oncology. Our HCC [hepatocellular carcinoma] franchise is quite healthy in those markets, for example. If you look at the launch of Xofigo in Japan, we're doing very well there. And when you think about Stivarga [approved globally in multiple indications including metastatic colorectal cancer and gastrointestinal stromal tumors], we just received FDA approval for Stivarga in second-line HCC, but when we filed HCC with Stivarga we did it on a global scale, in all countries where we operate.

We're trying to speed up those approvals and have strategies where we can do clinical trials that are truly global in scope. Sometimes it would make sense to focus in the US where the FDA may grant a priority review in a high unmet medical need, like we've

> done with our refractory follicular lymphoma drug copanlisib. We'll know later this year if FDA approves it.
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> This type of regulatory opportunity is not available in all countries, but we're following it up with two large Phase III trials for the global filings.